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Short communications and technical notes

A new method to visualize and to spare the ureters during SBRT for oligo metastatic patients

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ABSTRACT

This article describes a ureter-sparing procedure used to treat lymph node metastases with SBRT. We delivered 35 Gy in 5 fractions of 7 Gy to patients with lesions located less than 7 mm from the ureters using a urography CT scan for planification. Two dosimetry plans were created, one using a CT scan urography-based contour and the other using the native phase. PTV coverage were not statistically different but this technique was able to significantly reduce median delivered Dmax to the ureters. These preliminary results demonstrate the feasibility of locating the ureters in a planning CT scan to protect them.

Introduction

Ureteral damage following abdominal or pelvic irradiation is a rare complication, identified in approximately 1 to 3% of patients treated with external beam radiation therapy (RT) and brachytherapy for cervical cancer [1–3] and in 1.3% of patients treated for prostate cancer (PCa) before the era of intensity-modulated radiation therapy [4]. Notably, ureteral stricture or stenosis can manifest with pain, hematuria, urinary tract infections, hypertension, and renal failure, and can ultimately be life-threatening [5]. In some studies, ureteral complications are often followed by clear signs of radiation cystitis [2]. Because the event is rare, it is difficult to associate it with factors that increase the likelihood of harm, and there are no dose–response data for the development of this complication, which can occur several years after RT.

For example, in a preclinical study, 20 Gy to the ureter of a dog in a single intraoperative fraction caused ureteral obstruction [6]. However, there is no solid evidence of human ureteral tolerance to such spectrum of high-dose RT.

Nowadays, stereotactic body radiation therapy (SBRT) delivers high doses of radiation, allowing more dose to be delivered to the tumor without increasing the dose to organs at risk, provided they are well protected. The literature on ureteral preservation and dose tolerance while using SBRT is scarce. In addition, anatomically, ureters are tubular narrow structures that are difficult, if not impossible, to visualize without an intravenous urography scan [7].

In this article, we describe the possibility to spare the ureters from high dose irradiation by using an intravenous urography technique. This technique was applied to patients with prostate cancer lymph node metastases that were in close contact with the ureter.

Material and methods

Patients' inclusion criteria

Due to the limited number of patients (less than five), approval by the Ethic Committee of Switzerland was not required. The patients consented to undergo a standard urography CT scan.

Patients with asymptomatic PCa were eligible if they had biochemical recurrence after primary PCa treatment with curative intent, five or fewer extracranial metastatic lesions visible on Gallium-68-prostate-specific membrane antigen (^{68}Ga-PSMA) positron emission tomography (PET) / computed tomography (CT) and at least one being located at less than 7 mm from the ureter. Approximately 30 days before starting SBRT, patients underwent magnetic resonance imaging (MRI) and ^{68}Ga-

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PSMA-PET/CT to identify the metastatic lesion in both imaging modalities. Patients were treated with the intention of eliminating all visible metastatic deposits with ablative doses of SBRT. The secondary objective was to reduce the maximum dose received by the ureters as well as other organs-at-risk (OARs). Patients were required to have normal renal function, defined as an estimated glomerular filtration rate greater than 60, no hyperthyroidism, and no known iodine allergy.

Preparation for irradiation and treatment planning

Eight to ten days prior to the start of SBRT, patients underwent a native planning CT scan and at the same time a planning CT scan with intravenous contrast. For the urography phase the scan delay time was 4 min [7] (Fig. 1). Patients were required to have discontinued metformin treatment 24 h before the planning CT scan and were asked to have a good hydration (1.5 to 2 L per day) on the day of the scan and the next day to promote excretion of the iodinated contrast agent through the ureters.

Patients were scanned in the supine position with an arm/thoracic support (with both arms above the head; ThoraxSupportTM short, MacroMedics®, The Netherlands). The planning CT -scan acquisition parameters were as follows: tension, 120 kV; tube rotation time 0.5 s; tube current automatically modulated; helical pitch of 11; with a reconstructed image thickness of one mm (Multislice Helical CT scanner Aquilion LB, Toshiba®, Japan). Iodinated contrast (AccupaqueTM Iohexol, GE Healthcare® AG, Switzerland) was administered into the patient's vein via a dual head power injector (MEDRAD® Stellant CT injection system, Bayer Radiology AG, Germany). The parameters for contrast injection were as follows: contrast agent concentration 300 mg/I/mL, injection rate 3 mL/s, injection volume between 70 and 100 mL (depending on patient weight). When using a peripheral venous catheter less than 0.8 mm (22 Gauge) in diameter, we reduced the injection rate to 2 mL/s.

Contouring and dosimetry

The planning CT was rigidly registered with ^{68}Ga-PSMA-PET/CT and MRI to better identify the gross tumor volume (GTV) and OARs using Raystation treatment planning system (Raystation® 9.2 planning system software© Raysearch Laboratories AB, Sweden). The planning was performed in Accuray Precision® version 3.1. Treatment was delivered with the CyberKnife unit (Accuray®, Sunnyvale, USA), with XSIGHT® spine tracking system which enables the tracking of the spine without the need for implanted fiducials.

The GTV with automatically derived 3 mm expansion formed the planning target volume (PTV), no expansion margins were used for clinical target volume (CTV; GTV = CTV). All OARs near the target were drawn (e.g. bowel, rectum, sigmoid, bladder, femoral heads) and protected from high-dose irradiation. We did not delineate the kidneys in these patients because the target was below the aortic bifurcation. The ureters were contoured *in toto* on the urography CT scan (as they were not visible in any of the other images; e.g.: native CT, MRI, PET/CT) with

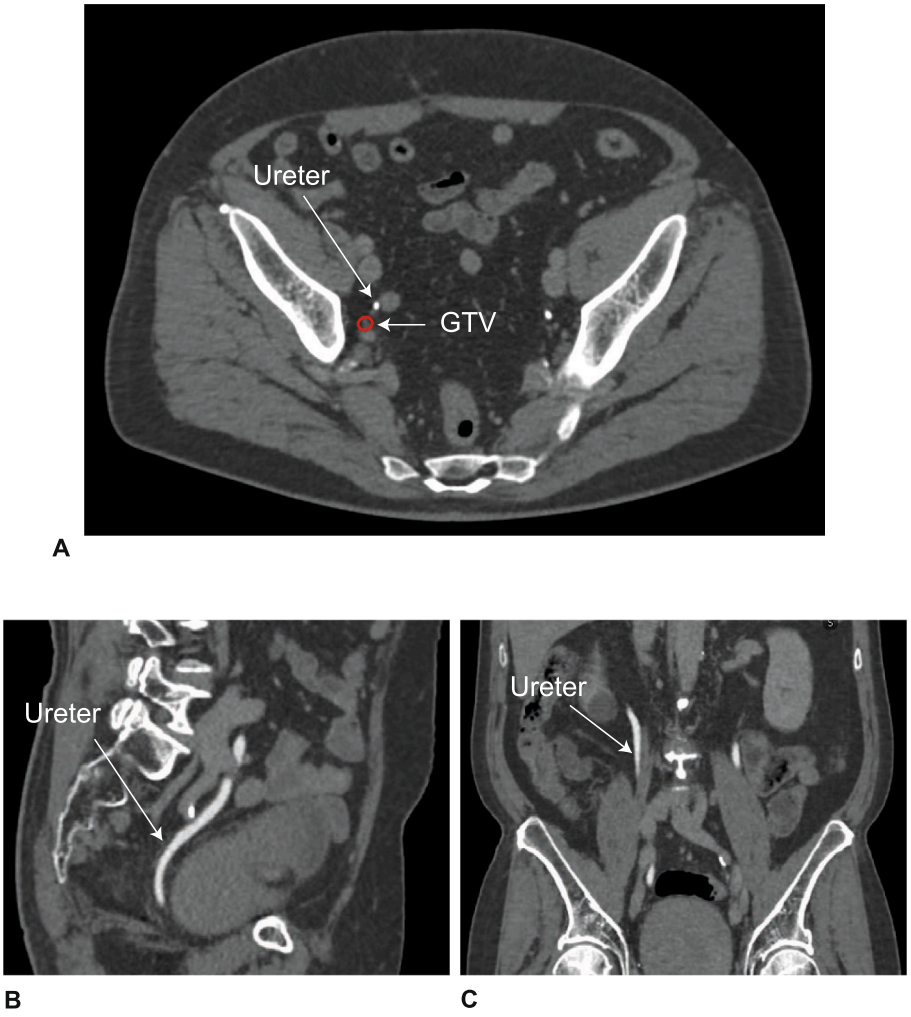

Fig. 1. CT scan images of the abdomen showing the ureters. Images were taken 4 min after injection of iodinated contrast medium. **A)** Axial view. Distance from ureter to GTV = 4 mm. **B)** Sagittal view. **C)** Coronal view. GTV = Gross tumor volume.

a 2 mm planning organ at risk volume (PRV) in order to account for registration errors. The urography CT was then fused with the native CT scan and the ureters were transferred to the native CT in order to prepare two plans: one sparing the ureter (due to its correct visualization) and another without ureter sparing (due to lack of visualization).

We prescribed 35 Gy in 5 fractions of 7 Gy at the 80% isodose line. There were no more than 5 days between treatment fractions.

Biologically effective dose to the PTV was expected to be greater than 100 with an α/β ratio of 3 Gy which has been considered ablative for PCa [8]. To allow for gradients and maximize PTV doses, the limit of dose heterogeneity within the PTV was 43.75 Gy, according to the prescription. At least 95% of the PTV and 100% of the GTV had to be covered by the prescribed dose. Dose constraints for OARs were applied based on previous publication [9], briefly: bowel V38 less than 0.5 cc, rectum 1 cm^3 less than 38 Gy and bladder 1 cm^3 less than 41 Gy. We attempted to obtain the lowest possible maximum dose to the ureter without compromising the PTV coverage.

For comparison purposes, two dosimetry plans were created, one using delineation based on urography CT scan that allowed good visualization of the ureters in order to apply full protection, and the other using the native CT scan (without visualization and protection of the ureter). For PTV and all OARs, we compared the median mean dose (Dmean) and median maximum dose (Dmax) administered by these two plans.

P-value was calculated using an unpaired *t*-test with Welch's correction.

Results

A total of four patients and five metastatic lesions were treated and evaluable for study endpoints. The median age was 73.5 years (range, 67–74 years). The median PSA level at baseline was 5.95 μg/mL (range, 0.5–9.2 μg/mL). The median PTV volume was 1.84 cm^3 (range, 0.73–13.3 cm^3). The mean distance between the target and the ureter was 3 mm (range, 2–7 mm). The median RT treatment duration was 11 days (range, 6–17 days). All patients were able to complete their treatments. Androgen deprivation therapy was given to one of four patients.

The median dose covering 95% of the PTV was 36.76 Gy (range 35.47–37.04 Gy) without urography CT and 36.47 Gy (range 35.00–37.33 Gy) with urography CT visualization technique (P = 0.5635). Table 1 shows the planned versus the delivered doses to the OARs. Importantly, there was no statistically significant difference in the Dmean administered to the ureters (Dmean 3.21 Gy without sparing *vs.* 2.35 Gy with sparing, P = 0.188). However, we were able to reduce significantly the median Dmax administered to the ureters using a urography CT-based delineation approach (Dmax 33.55 Gy without visualization of the ureter *vs.* 28.12 Gy with good ureter visualization on the urography-based plan, P less than 0.02, Fig. 2).

Table 1
Dosimetry analysis for organs at risk.

OARs*	Mean dose		Maximum dose	
	Without sparing technique (lack of visualization of the ureter) Gy (range)	With sparing technique (visualizing the ureter with the use of urography CT) Gy (range)	Without sparing technique (lack of visualization of the ureter) Gy (range)	With sparing technique (visualizing the ureter with the use of urography CT) Gy (range)
Ureters	3.21 (1.99–3.89) **P = 0.19**	2.35 (1.71–3.18)	33.55 (31.41–37.07) **P = 0.02**	28.12 (23.26–32.23)
Bowel	0.38 (0.30–1.77) **P = 0.98**	0.36 (0.32–1.81)	17.52 (7.32–35.85) **P = 0.98**	17.63 (10.00–35.19)
Rectum	0.19 (0.01–0.46) **P = 0.89**	0.21 (0.01–0.44)	1.02 (0.01–4.58) **P = 0.99**	1.14 (0.01–3.74)
Bladder	0.11 (0.01–2.17) **P = 0.91**	0.06 (0.01–1.92)	1.05 (0.01–9.99) **P = 0.94**	0.28 (0.01–9.76)

* OARs = Organs at risk

Discussion and conclusion

The primary goal of curative SBRT is to maximize tumor control while minimizing the short- and long-term negative side effects of radiation. Therefore, every effort should be made to ensure precise delivery of SBRT using all available technical means. Without a urography-based CT scan, the ureters may be jumbled with the target volume and would therefore receive full radiation dose. Here, we present a new and feasible method that facilitates visualization and sparing of the ureters during SBRT without compromising tumor coverage. Although these are preliminary results, we demonstrated a statistically significant reduction in the ureter Dmax (median dose reduction 16.3%, range 5.2–28.3%) with only 5 lesions irradiated. This significant reduction in the ureter Dmax was observed when irradiating small PTVs (less than 13.3 cm^3) located less than 7 mm from the ureter, and future research will be required to confirm whether the same benefit exists when irradiating larger tumors. Similarly, it is assumed that the Dmax to the ureter and other OARs would be particularly high when the distance between the organ and the GTV/PTV is short, and thus the greatest benefit of this technique would most likely be observed if the distance between the GTV and the ureter is less than 7 mm and 1cm in order to reduce the Dmax to the organ.

Limitations of this study include the small number of patients, the lack of long-term follow-up to evaluate late toxicity, and the fact that ureteral peristalsis may not be captured by the image-guided RT technique, which increases the intrafraction uncertainty of the delivered dose. Another shortcoming of the present study is the possibility of image fusion errors because the MRI and PET/CT were not performed in the same identical position as the planning CT.

Nonetheless, our findings highlight the importance of combining all imaging modalities (MRI, PET/CT, and planning CT) to reduce the possibility of uncertainties in target volume delineation. On the other hand, because the urography CT scan was performed in the same position as the native CT scan only four minutes later, we assumed the set-up error between these two images was less than 2 mm.

Overall, however, we demonstrate that a urography CT scan is a feasible and a safe method to spare the ureters during SBRT. However, it is worth noting that with our ureter sparing technique, we observed a slight, non-significant increase in Dmax and Dmean to rectum and bowel; we believe that this is part of the spatial trade-offs that are required when computing the dose distribution to a given target. Relaxing some constraints is a necessary preconditioning to improve other objectives, and thus fine-tuning the plan optimization should allow for the right balance of OAR sparing and PTV coverage.

Future research is needed to confirm that this technique ensures adequate dose coverage of the target as shown in this small group of patients. Although there are insufficient data in the literature on dose to the ureters during SBRT, our data may open the door for future studies in this area.

Conflict of Interest:

Dr R. Moeckli reports grants from Accuray Inc.

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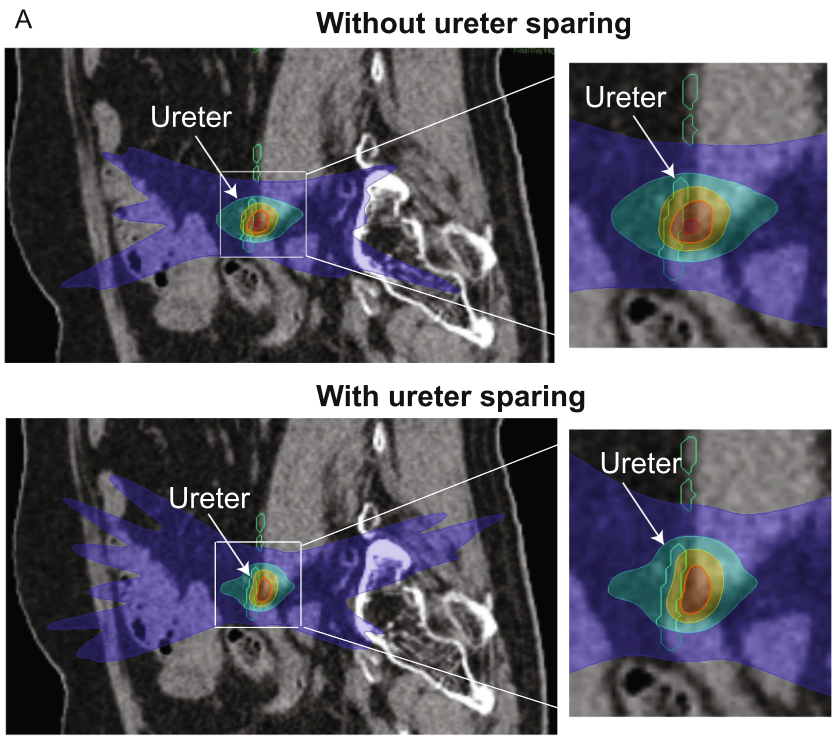

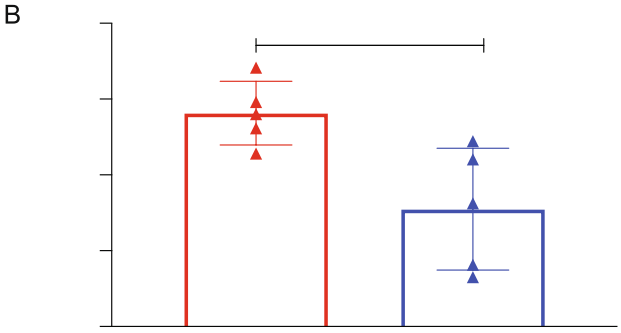

Fig. 2. A) Dosimetry of a patient with a metastatic iliac lymph node treated with 35 Gy in 5 fractions of 7 Gy, sagittal view. PTV and GTV are covered by 98% and 100% of the prescribed dose, respectively. Red: 42 Gy isodose line. Orange: 36 Gy isodose line. Yellow: 27 Gy isodose line. Light blue: 13 Gy isodose line. Dark blue: 1 Gy isodose line. **B)** Bar plot depicts median Dmax (±SEM), dots are individual patient's values, *P*-value was calculated using an unpaired *t*-test with Welch's correction. PTV = Planning target volume. GTV = Gross tumor volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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Data availability statement for this work

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

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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