Received:
03 September 2019

Revised:
07 November 2019

Accepted:
19 November 2019

<https://doi.org/10.1259/bjr.20190760>

Cite this article as:

Tsang YM, Vignarajah D, McWilliam A, Tharmalingam H, Lowe G, Choudhury A, et al. A pilot study on dosimetric and radiomics analysis of urethral strictures following HDR brachytherapy as monotherapy for localized prostate cancer. *Br J Radiol* 2020; **93**: 20190760.

FULL PAPER

A pilot study on dosimetric and radiomics analysis of urethral strictures following HDR brachytherapy as monotherapy for localized prostate cancer

¹YAT MAN TSANG, PhD, ²DINESH VIGNARAJAH, ³ALAN MCWILLIAM, ¹HANNAH THARMALINGAM, ¹GERRY LOWE, ³ANANYA CHOUDHURY and ^{1,3}PETER HOSKIN

¹Mount Vernon Cancer Centre, Northwood, United Kingdom

²Sunshine Coast University Hospital, Queensland, Australia

³Division of Cancer Sciences, Faculty of Biology Medicine and Health, University of Manchester, Manchester, United Kingdom

Address correspondence to: Dr Yat Man Tsang

E-mail: yatmantsang@nhs.net

Objective: A cohort of high dose-rate (HDR) monotherapy patients was analyzed to (i) establish the frequency of non-malignant urethral stricture; (ii) explore the relation between stricture formation with the dose distribution along the length of the urethra, and MRI radiomics features of the prostate gland.

Methods: A retrospective review of treatment records of patients who received 19Gy single fraction of HDR brachytherapy (BT) was carried out. A matched pair analysis used one control for each stricture case matched with pre-treatment International Prostate Symptom Score (IPSS) score, number of needles used and clinical target volume volume for each stricture case identified.

For all data sets, pre-treatment T_2 weighted MRI images were used to define regions of interests along the urethra and within the whole prostate gland. MRI textural radiomics features—energy, contrast and homogeneity were selected. Wilcoxon signed-rank test was performed to investigate significant differences in dosimetric parameters and MRI radiomics feature values between cases and controls.

Results: From Nov 2010 to July 2017, there were 178 patients treated with HDR BT delivering 19Gy in a single

dose. With a median follow-up of 28.2 months, a total of 5/178 (3%) strictures were identified.

10 patients were included in the matched pair analysis. The urethral dosimetric parameters investigated were not statistically different between cases and controls ($p > 0.05$). With regards to MRI radiomics feature analysis, significant differences were found in contrast and homogeneity between cases and controls ($p < 0.05$). However, this did not apply to the energy feature ($p = 0.28$).

Conclusion: In this matched pair analysis, no association between post-treatment stricture and urethral dosimetry was identified. Our study generated a preliminary clinical hypothesis suggesting that the MRI radiomics features of homogeneity and contrast of the prostate gland can potentially identify patients who develop strictures after HDR BT. Although the sample size is small, this warrants further validation in a larger patient cohort.

Advances in knowledge: Urethral stricture has been reported as a specific late effect with prostate HDR brachytherapy. Our study reported a relatively low stricture rate of 3% and no association between post-treatment stricture and urethral dosimetry was identified. MRI radiomics features can potentially identify patients who are more prone to develop strictures.

INTRODUCTION

High dose-rate brachytherapy (HDR BT) can accurately deliver a conformal high radiation dose to prostate cancer (PCa) with a rapid dose drop off, minimizing doses to the adjacent normal organs. With increasing interest in using HDR BT in PCa management, different hypofractionated monotherapy schedules have been suggested to be a safe and effective treatment option for patients with organ-confined PCa.^{1–10}

One of the commonest late effects after PCa HDR BT is urethral stricture with an incidence rate up to 15%.¹¹ However, limited data have been reported on the causes of the post-radiotherapy stricture especially the relationship between urethral dose–volume constraints and radiation-induced stricture after HDR BT.^{12,13}

MRI is fundamental to PCa management with the information that it can provide for screening and diagnosis.^{14,15} Features of the MRI scans can be analyzed at a millimeter

level to extract data which can be used to characterize the tumour in detail. Radiomics is defined as the high-throughput extraction of a large number of advanced quantitative features from radiographic images generating high-dimensional data that can be mined in combination with clinical and molecular features to enhance decision support.^{16,17} The central dogma of the radiomic approach lies in the ability of extracted imaging features to capture distinct variations in tumour phenotype, defined as tumour "habitats" that could have diagnostic, predictive or prognostic power.¹⁸ Radiomic studies using prostate MRI have shown radiomics features to be related to both tumour physiology, allowing for automated detection of tumours,^{19,20} as well as disease aggressiveness and increased risk of recurrence.^{21–23}

Against this background, a cohort of PCa patients receiving a single dose of HDR BT monotherapy at a single institution has been analyzed to (i) establish the frequency of non-malignant urethral stricture; (ii) explore the relationship between stricture formation and the dose distribution along the length of the urethra, and MRI radiomics features of the prostate gland.

METHODS AND MATERIALS

Patients, who were fit for general anaesthesia and able to give informed consent, with histologically confirmed staging T1 to T3b localized PCa and serum prostate-specific antigen $<40 \mu\text{g l}^{-1}$ were eligible for HDR BT delivering a single dose of 19 Gy. This work was undertaken as a service evaluation and all patients provided written informed consent for their data to be used in this study.

All patients had HDR BT delivered following TRUS-guided transperineal implantation of flexible afterloading interstitial catheters (Varian part GM11007570, plastic, 200 mm long, 2 mm diameter) as previously described.²⁴ Patients were treated with a single exposure using a ¹⁹²Iridium HDR afterloading system on the day of implant. After completion of treatment, implant catheters were removed and the patient discharged

either the same day or the following day. All HDR BT plans were optimized using the PTV and urethra dose constraints as shown in Table 1.

All patients were treated under the same HDR BT protocol and imaged in a Siemens MAGNETOM C! 0.35T MRI scanner (Siemens Healthineers, United Kingdom). The MRI scanner was maintained under a comprehensive quality assurance (QA) programme (daily check of functionality, image geometry and distortion, and signal to noise ratio; quarterly check of signal uniformity and verification of sequence parameters in protocols; biannually assessment of system tuning and magnet shimming).

Prior to the HDR BT, pre-treatment high-resolution axial T_2 weighted (T_2W) anatomic images were acquired at 12 bits depth [turbo spin echo (TSE); echo time (TE): 121 ms; repetition time (TR): 4000 ms; $512 \times 432 \times 20$ matrix] post-implantation in order to identify HDR interstitial catheters and urinary catheters. The MRI images were used to define the urethra (extending from the bladder to the external urethral meatus) and regions of interest (ROIs) in the prostate gland. The clinical target volume (CTV) was defined as in the GEC/ESTRO guidelines to include the whole prostate capsule, extended to cover extracapsular and seminal vesicle disease if diagnosed on staging MRI.²⁵ The planning target volume (PTV) was a 3 mm volumetric expansion from the CTV, constrained to the anterior rectal wall. Using the urinary catheter as a surrogate, the urethral contour was defined as an 8 mm cylinder volume centralized on the catheter. With the pre-treatment MRI, the whole urethra was divided into prostatic urethra and membranous urethra retrospectively by a single observer for the purpose of analysis as illustrated by Figure 1. The prostatic urethra was further divided into inferior, mid and superior equal thirds. The prostatic urethra was defined from the base of the bladder to the prostate apex. The membranous urethra was contoured from the apex of the prostate to the bulb of the penis.

Table 1. summarizes the PTV and urethra planning dose constraints used for the HDR BT plans

Dose constraints	Patients with stricture (<i>n</i> = 5)	Patient with no stricture (<i>n</i> = 5)	<i>p</i> - value
	Median value (range)	Median value (range)	
PTV V19Gy (100%)>90%	92.5% (92.3–99.1)	93.2% (93.1–98.5)	0.75
PTV V28.5Gy (150%)<55%	27.1% (19.5–34.2)	29.4% (27.7–34.9)	0.29
PTV V38Gy (200%)<20%	8.5% (4.5–12.3)	11.2% (9.4–12.6)	0.20
Whole urethra D10% < 22 Gy	20.50 (16.9–20.9)	21.10 (17.0–23.3)	0.22
Whole urethra D30% < 20.8 Gy	19.90 (16.4–20.7)	19.3 (16.5–21.2)	0.17
Whole urethra Dmax < 28.5 Gy	22.10 (18.4–24.2)	22.20 (17.4–31.7)	0.72

HDR BT, high dose-rate brachytherapy; PTV, planning target volume.

Figure 1. Illustrating the whole urethra (red), membranous urethra (green), prostatic urethra (yellow), lower third prostatic urethra (orange), middle third prostatic urethra (pink) and upper third prostatic urethra (blue) as 1a, 1b, 1c, 1d, 1e and 1f respectively

Haralick textural radiomic features of homogeneity, contrast and energy were selected for evaluation. These features were selected as those presented in the literature as being stable in analyzing MR imaging of the prostate.^{21–23} The T_2 weighted MR image was acquired with a spatial relationship defined with the relative direction q at angles 0° , 45° , 90° , 135° in respect to the xy plane of the MRI co-ordinate map (Table 2).²³ A spatially invariant matrix was created using the average counts of the four angles; these images were available for analysis. Features were derived from the three-dimensional grey level co-occurrence matrix (GLCM) of this image and the final values subsequently used for analysis. The ROI for radiomics extraction was defined as the whole prostate CTV with subtraction of the urinary catheter. GLCM feature extraction was performed independently from the ROI using Pyradiomics (Python v. 3.4). As all patients were imaged on the

same scanner for all examinations, no normalization technique was required.

Under the approval of the institutional research ethics board, a retrospective review of treatment records of PCa patients who received the single fraction of HDR BT was carried out to establish the post-treatment toxicity. Patients were seen at 1, 3 and 6 months after treatment, 6 monthly intervals thereafter to 5 years and then annually. Associations with dosimetric parameters and MRI radiomics features were evaluated by performing a matched-pair analysis with one control matching pre-treatment IPSS score, number of needles used for insertion and CTV volume for each case of stricture. A stricture was defined by a patient who was symptomatic, requiring dilatation or catheterization for stricture confirmed on cystoscopy. This definition

Table 2. Haralick features evaluated and corresponding GLCM calculation

Haralick feature	GLCM calculation
Homogeneity	$\sum_{i,j} P(i,j) / (1 + i - j)$
Energy	$\sum_{i,j} P(i,j)^2$
Contrast	$\sum_{i,j} P(i,j) \cdot i - j ^2$

GLCM, grey level co-occurrence matrix.

As defined by Wibmer et al, two pixels within an image can be separated by a displacement vector of δ pixels along angle θ .²³ For an image of G grey levels, GLCM is defined as $P(i,j|\delta,\theta)$. The entry (i,j) represents the number of times the combination of grey levels i and j occur in two pixels in the image, that are separated by a distance of δ pixels along angle θ . The distance δ from the center voxel is defined as the distance according to the infinity norm and in this study was one pixel.

is equivalent to Grade II or higher using the Common Terminology Criteria for Adverse Events v. 4.0 protocol. All stricture cases were matched with controls receiving the same dose fractionation schedule (19 Gy in one dose), pre-treatment IPSS score, number of needles used for insertion and CTV volume. Wilcoxon signed-rank test was performed to investigate significant differences in the baseline demographic variables, dosimetric parameters and MRI radiomic feature values between stricture cases and controls. For all tests, a p -value of ≤ 0.05 was considered statistically significant. Statistical analysis was performed with SPSS v. 22.0 (IBM Corp., Armonk, NY).

RESULTS

From Nov 2010 to July 2017, there were 178 patients treated with HDR monotherapy of 19 Gy in a single dose. With a median follow-up of 28.2 months (range 12–48 months), a total of 5/178 (3%) stricture cases was identified. The median time to stricture formation was 12 months (range 12–48 months).

For the matched-pair analysis, five controls were selected for being comparable to the stricture cases, all cases being intermediate risk according to the D'Amico criteria.²⁶ For all 10 cases, the median CTV and whole urethra volumes were 41.0 cc (range 31.9–47.5cc) and 2.2 cc (range 1.6–3.8cc) respectively. There were no statistical differences in age, pre-treatment IPSS score, number of needles used, CTV and urethra volume sizes between the two groups of patients with and without strictures ($p > 0.05$).

As described in Table 1, all 10 cases achieved the PTV and urethra planning objectives and there were no significant differences found between two groups. Reviewing the six ROIs of the urethra (whole, membranous, prostatic, inferior-, mid- and superior-third prostatic), none of the urethral dosimetric parameters investigated were statistically different between the stricture cases and controls as indicated in Table 3.

With regards to MRI radiomics feature analysis, the comparisons between the stricture and control cases are illustrated in Table 4. Significant differences were found in contrast and homogeneity between the stricture cases and controls ($p < 0.05$). However, this did not apply to the energy feature ($p = 0.28$).

DISCUSSION

In the evaluation of treatment for prostate cancer it is important to consider quality of life and radiotherapy-induced genitourinary morbidities alongside tumour control.²⁷ Urethral stricture is a significant late effect of any PCa radiotherapy.¹² In one series of 1903 patients, the post-treatment stricture rate was found to be higher after HDR BT (11%) compared with low dose rate BT (4%) and external beam radiotherapy (2%).²⁷ Overall, the incidence of urethral stricture in the literature after HDR BT ranges from 0 and 14%, with the majority of studies reporting rates of 4–9% at 5 years.¹¹ One of the aims of the present study was to investigate the frequency of non-malignant urethral stricture of PCa patients receiving a single dose of HDR BT. In this series, a relatively low stricture rate of 3% was found. It has been suggested that there is a higher risk of stricture formation with an increasing fraction size, implying a potential disadvantage of adopting a high single dose schedule for HDR BT.^{11,28} The median time to the development of stricture was 12 months in this cohort which is in keeping with other HDR BT monotherapy treatment schedules where the median time to development of stricture ranged from 4 to 36 months.¹¹

Pre-treatment IPSS, number of needles used, prostate gland volumes and the volume of prostate gland receiving 150% of the HDR BT prescription dose (V150%) have been reported as strong predictors of radiation induced stricture.²⁹ As illustrated in Tables 1 and 3, there were no statistically significant differences in these parameters between the control and stricture cases in this series.

No significant differences in urethra dosimetric parameters were found between the stricture cases and control in this single fraction cohort,¹³ which is similar to our findings in patients receiving multifractions HDR BT. The majority of strictures after HDR BT occur in the bulbomembranous urethra.^{11,28} However, in this study no differences in the doses received by the membranous urethra were seen between stricture cases and controls: median D10% of 18.5 Gy (stricture) vs 18.3 Gy (no stricture). A systematic review has suggested a threshold dose for urethral stricture with a urethra of 109 Gy EQD2 (equivalent dose at 2 Gy per fraction) with a 10% stricture rate above this dose and higher risk of urinary pain with a urethra mean dose of 91 Gy EQD2.¹² Using the same assumption of α/β 3 Gy for the late complication, the maximum D10% and mean dose of membranous urethra were 19.5 Gy (BED_{2Gy} 87.5 Gy) and 17.5 Gy (BED_{2Gy} 71.6 Gy) respectively among all 10 cases in this study. These lower than threshold urethra dosimetric values might contribute to the favourable outcome of stricture rate from this study; however, the validity of the linear quadratic equation as such high doses per fraction is uncertain and the dose equivalence may be inaccurate.

Multiparametric MRI is the preferred modality for PCa diagnosis and staging with its high sensitivity and specificity.^{14,15} The wealth of data which this provides facilitates research into radiomics features, with the possibility of defining new predictive and prognostic parameters which can be used to aid PCa clinical decision-making.^{16–23} For example, application of radiomics feature analysis on pre-radiotherapy T_2W MRI has

Table 3. Table 3 demonstrates the baseline demographic variables and urethra dosimetric parameters between stricture cases and controls

		Patients with stricture (<i>n</i> = 5)	Patient with no stricture (<i>n</i> = 5)	<i>p</i> value
		Median Value (range)	Median Value (range)	
Baseline demographics	Age (years)	72.5 (62.3–77.0)	68.4 (63.7–73.5)	0.44
	Pre-treatment IPSS	8 (7–10)	8 (7–10)	0.94
	Number of needles used	21 (19–30)	20 (19–28)	0.37
	CTV volume (cc)	40.9 (26.4–46.4)	41.1 (31.9–47.5)	0.39
	Whole urethra volume (cc)	2.2 (1.7–3.8)	2.1 (1.6–2.7)	0.31
Urethra D10% (Gy)	Membranous	18.5 (14.8–19.6)	18.3 (14.3–19.5)	0.25
	Prostatic	20.6 (16.9–20.9)	21.2 (17.0–23.7)	0.22
	Inferior third prostatic	20.3 (16.1–20.9)	20.8 (16.3–21.6)	0.58
	Mid third prostatic	20.3 (17.0–21.0)	20.8 (16.7–21.5)	0.32
	Superior third prostatic	20.8 (16.7–21.2)	21.0 (17.2–25.9)	0.26
Urethra D30% (Gy)	Membranous	17.1 (14.2–18.8)	16.9 (13.5–17.9)	0.20
	Prostatic	20.0 (16.5–20.7)	20.7 (16.6–21.4)	0.18
	Inferior third prostatic	19.8 (15.9–20.7)	20.0 (15.9–21.2)	0.77
	Mid third prostatic	19.8 (16.8–20.7)	20.2 (16.4–21.2)	0.46
	Superior third prostatic	20.4 (16.2–20.9)	20.6 (17.0–23.4)	0.18
Urethra maximum dose (Gy)	Membranous	20.2 (19.5–22.8)	20.0 (15.5–22.3)	0.20
	Prostatic	22.1 (18.4–24.2)	22.1 (17.4–31.7)	0.72
	Inferior third prostatic	21.1 (18.4–22.8)	21.8 (17.2–24.2)	0.86
	Mid third prostatic	21.4 (18.3–23.9)	22.0 (17.1–23.0)	0.66
	Superior third prostatic	21.7 (17.7–23.3)	21.6 (17.4–31.7)	0.60
Urethra mean dose (Gy)	Membranous	16.5 (13.1–17.5)	15.8 (12.8–16.4)	0.21
	Prostatic	20.1 (16.7–20.5)	20.4 (16.2–21.0)	0.63
	Inferior third prostatic	19.9 (17.0–20.5)	19.9 (15.6–20.7)	0.29
	Mid third prostatic	20.6 (16.8–21.1)	20.0 (16.2–21.0)	0.51
	Superior third prostatic	19.7 (16.0–20.3)	20.1 (16.8–22.9)	0.65

CTV, clinical target volume.

suggested that radiomics can be used to predict radiotherapy induced rectal toxicity in PCa patients.³⁰ No previous study has been done to investigate the correlation between MRI radiomics

and stricture rate after HDR BT. As indicated in Table 4, there are statistically significant differences in the MRI radiomics features of homogeneity and contrast between stricture and control cases

Table 4. Demonstrates the MRI radiomics features between stricture cases and controls

		Patients with ≥Grade II stricture (<i>n</i> = 5)	Patient without ≥Grade II stricture (<i>n</i> = 5)	<i>p</i> -value
		Median value (range)	Median value (range)	
MRI radiomics features	Energy	0.0036 (0.0020–0.0060)	0.0018 (0.0017–0.0053)	0.28
	Contrast	30.1 (25.9–42.1)	50.3 (30.1–68.4)	0.04
	Homogeneity	13.7 (11.8–17.7)	22.1 (14.4–30.7)	0.04

before radiotherapy. In particular, the homogeneity feature has a slightly narrower range in the stricture group implying that it might be possible to use this parameter to identify those more prone to develop strictures after HDR BT.

With regards to the potential impact of the needles placement, the extracted radiomics features would have captured the texture properties of the prostate gland incorporating a spatial aspect of the implanted needles. Additionally, radiomics features were expected to incorporate any localized trauma, and extent of trauma, in the prostate gland due to the insertion. This study suggested that analyzing the radiomics of the entire prostate gland with needles *in situ* could better predict which patients would display a urethral stricture than using conventional analysis techniques on patient's specific clinical and treatment parameters. Future work is needed to include the analysis the pre-treatment MR, in order to investigate the impact of the needle placement fully.

The strengths of the study include the use of Pyradiomics, an open-source package compliant with accepted standards. It is increasingly recognized that all radiomic studies should now be conducted with open-source software to foster consistency, improve methodological transparency and facilitate further interinstitutional evaluation of published works.³¹ Reproducible and consistent contouring is critical to robust radiomic evaluation. Whilst the potential for variability is acknowledged in this study, ROI delineation was performed according to a defined protocol for all patients to mitigate this. Finally, all patients were imaged on the same MR scanner using the same protocol under a comprehensive QA programme; therefore no normalization or standardization technique was required with respect to radiomic feature extraction. Haralick textural radiomics features of homogeneity, contrast and energy were selected for evaluation as they

have been validated as robust parameters for radiomic analysis of prostate MRI in the literature.^{21–23} Whilst there is no clear basis why such features would predict for urinary stricture, it was felt that the numbers evaluated were too small to allow for reliable processing of a large number of hypothesis-generating features.

It is acknowledged that the limitations of our study are its retrospective nature, the small number of events and the fact that the data are from a single institution. With the low number of episodes of stricture identified, variations in the late toxicities could be due to different patient sensitivities to HDR BT instead of the parameters investigated in this study. It is also possible that the actual stricture rate of our cohort is underestimated owing to the varying stricture definitions by different urologists and the practicalities of capturing these events.²⁸

This study is the first of the kind suggesting that the MRI radiomics features of homogeneity and contrast of the prostate gland identified patients who develop strictures after HDR BT. Extracting these radiomics features from the staging MR can potentially benefit prostate cancer patients by providing an extra risk stratification. Although the sample size is small, this preliminary clinical hypothesis of using radiomics as a prognostic tool warrants further validation in a larger independent sample size under a multicentre randomized trial setting.

ACKNOWLEDGMENT

We thank all the patients who participated in this study, and the doctors, nurses, radiographers and physicists at Mount Vernon Cancer Centre. We acknowledge the support of Dr Roberto Alonzi, Dr Peter Ostler and Dr Robert Hughes. Professor Peter Hoskin, Professor Ananya Choudhury and Dr Alan McWilliam are supported by the Manchester National Institute of Health Research Biomedical Research Centre.

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