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ARTICLE

Prostatic dystrophic calcification following salvage cryotherapy for prostate cancer – an under-reported entity?

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ABSTRACT

Background: Salvage cryoablation (SCA) is an accepted treatment for radio-recurrent prostate cancer with well-established oncological and functional outcomes. Based on one of the longest reported prospective follow-ups in the literature (median 12 years) on 187 patients, this study reports what appears to be an under-appreciated finding in eight patients with dystrophic calcifications (DC) of the prostate following SCA, causing severe bladder outlet obstruction.

Materials and methods: Between 1995 and 2004, 187 patients underwent SCA, with a median follow-up of 12 years. This database was reviewed for functional and oncological outcomes and DC were evaluated.

Results: Functional data was available in 85 patients, amongst whom eight patients were found to develop DC (9.4%) proven when the patients presented with urinary difficulties and attempted transurethral resection was undertaken for bladder outlet obstruction. Mean time for emergence of significant symptoms of bladder outlet obstruction was 8.6 years from SCA (standard deviation (SD) = 6 years). All eightpatients required permanent drainage (seven suprapubic catheters, one nephrostomy). All patients with DC experienced biochemical recurrence (BCR), compared to 57.1% of the patients with no DC ($p = 0.01$).

Conclusion: DC following SCA appears to be an under-reported late adverse effect which may only become evident with long follow-up, and should be included in preoperative counselling.

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Introduction

Cryotherapy for prostate cancer, first introduced in the 1960s, is commonly used as an ablative therapy for treatment of prostate cancer either in the primary or salvage settings [1,2]. The main mechanism of action is tissue necrosis first described by Cooper in 1964 [3]. Treatment had been delivered to the entire gland but, more recently, focal therapy to affected regions has become popular. Salvage cryoablation (SCA) of the prostate is an accepted local treatment option for biochemical recurrence (BCR) after radiotherapy [2,4,5]. The long-term oncological outcomes of SCA have been reported with disease-free survival (DFS) of 39% at 10 years [4], and up to 64% if pre-salvage serum prostate specific antigne (PSA) was <5 ng/ml. Notable complications following SCA include incontinence of various degrees (9–83%), urinary retention (3–55%), urethral sloughing (5–40.9%) and rectourethral fistula (0–3.3%) [6]. The complication rates have improved significantly with 3rd generation cryoablation devices.

We report on eight patients who developed dystrophic calcifications (DC) of the prostate following SCA during prolonged follow-up. Our mature database with 12 years of median follow-up allowed detection of this apparent late effect of SCA.

Materials and methods

Our prospectively maintained database consists of 187 patients who had undergone whole gland SCA following radiation failure between 1995 and 2004 with a median follow-up of 12 years. All 187 patients had histologically proven local cancer recurrence without clinical or radiographic evidence of metastatic disease. The salvage cryoablation procedure has been described elsewhere in detail by our group [7,8]. Briefly, two freeze–thaw cycles were administered using the Cryo-care – a second generation device with argon gas for cooling and helium for rewarming (Endocare Inc, Irvine, CA), with thermocouples for real-time intraoperative temperature monitoring and a Cook urethral warming catheter (Cook Medical, Bloomington, IN). Our database was reviewed for functional outcomes and patients with dystrophic calcifications were identified. Additionally, we assessed clinical parameters for these patients. Chi-square, *t*-test or non-parametric Mann-Whitney tests were used if applicable.

Results

Dystrophic calcifications of the prostate usually involve heavy depositions of calcium in the prostate (see Figure 1). These may in turn lead to obstruction, with the typical patient

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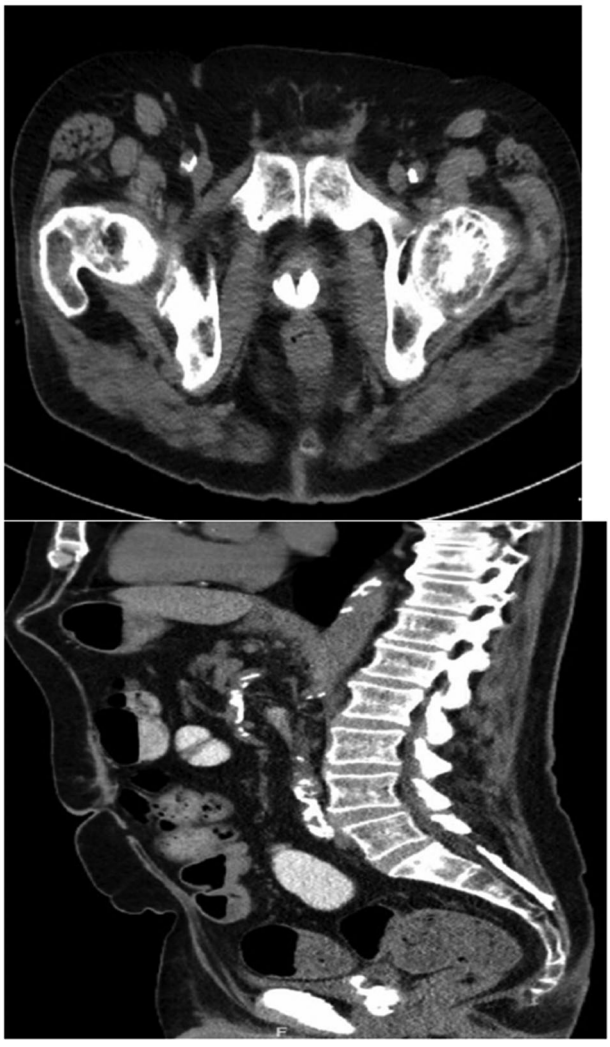

Figure 1. Axial and sagittal section of dystrophic calcification on CT scan.

seeking medical attention for obstructive urinary symptoms. Of 187 patients, functional data was available in 85 patients due to the tertiary referral nature of our practice. Of these, eight were found to have DC (9.4%) proven by cystoscopy or at the time of attempted transurethral resection. The mean time to diagnosis of DC was 8.6 years from SCA (standard deviation (SD) = 6 years). All had presented with obstructive urinary symptoms. DC was very extensive in all, rendering the prostate tissue hard and 'stone-like' and attempted transurethral resection and litholapaxy consistently failed to eradicate the calcified prostatic tissue, thus permanent suprapubic urinary drainage was necessary in all – seven suprapubic catheter and one nephrouretrostomy tube (the latter patient had ureteral obstruction in addition to DC). Oncological outcomes of our cohort are summarized in Table 1.

Noteworthy was that pre-radiotherapy PSA was significantly higher in the DC group (median 31 ng/ml vs 11.1 ng/ml; $p = 0.04$). However, PSA at BCR did not significantly differ between groups. All patients with DC experienced BCR, compared to 57.1% of the patients with no DC ($p = 0.01$). However, the interval between SCA and BCR was not different between the groups (3.4 years vs 3.17 for DC and no DC, respectively; $p = 0.88$). Patients with DC survived longer after SCA, with a mean overall survival of 17.7 years compared with 12.4 years in the no DC group ($p = 0.02$). We did not notice differences in age, pre-SCA PSA levels, time from radiotherapy to BCR, rate of metastatic disease, CRPC or overall survival between the two groups.

Discussion

Prior reports of dystrophic calcification of the prostate are scarce. Dru and Bender [9] reported the only reported case of DC following primary hemi-ablation cryotherapy. Though not reported specifically, this patient apparently also developed clinically obstructing DC as a late event following his cryotherapy. The case was managed with a transurethral resection of the prostate (TURP) with complete resolution. Jones et al. [10] reported on three patients with prostate cancer who developed DC after TURP followed by radiotherapy, suggesting radiotherapy plays a significant role in the pathogenesis process. Two other cases of DC formation in the prostate have been reported following non-cancer prostate manipulations. Zumstein et al. [11] reported on recurrent DC following simple TURP. Jeon et al. [12] reported DC after potassium-titanyl phosphate (KTP) laser vaporization of the prostate. In both reports, the interval between the procedure and occurrence of DC was relatively short, possibly suggesting different pathogenesis. DC may occur in other clinical scenarios, including vascular disease, collagen deposition disease, other rheumatologic diseases, post-radiation therapy and post-traumatic situations [13–15]. One proposed mechanism for DC is the calcification resulting from chronic inflammation and necrosis [13].

To our knowledge, this is the first reported, albeit small, series of dystrophic calcifications following salvage cryoablation of the prostate. Our reported rate of DC after SCA at 9.4% may be an underestimation, since some patients might have been asymptomatic with less extensive involvement and might remain undiagnosed. One possible explanation for this phenomenon not being reported previously is that only a mature dataset with an extended follow-up would allow detection of this condition of late onset (>8 years in our cases). The fact the the DC group survived longer compared to the non-DC patients is probably the reason for the development of DC as a late effect rather than an actual oncological outcome related to DC or its' pathophysiology, as the BCR rate among the DC group was higher. Another factor is the relatively short survival of this cohort (average age 69 at SCA) with advanced disease. The exact pathophysiology for the DC observed here is unclear, but presumably prior radiation therapy, chronic inflammation and necrosis may all be contributory [10,13].

Parenthetically, we have seen a case of DC several years following salvage high intensity focused ultrasound (HIFU). Hence, DC may be a complication of salvage ablative therapies in general, as opposed to specifically salvage cryoablation. One other potential factor in the pathogenesis is that these patients were all treated with an older cryo-technology (second generation instead of third generation). It seems unlikely, however, that DC was 'device-specific'.

Table 1. Patients characteristics.

	Overall ($n = 85$)	Dystrophic calcification ($n = 8$)	No dystrophic calcifications ($n = 77$)	p-value	95% CI for difference
Mean Age at SCA (SD)	69.6 (6.1)	68.1 (8.5)	69.7 (5.8)	0.23	−2.89-6.09
*Median Pre-radiation PSA (IQR)	11.1 (9.3)	31 (42.7)	11.1 (8.3)	0.042	
Pre-radiation Stage	78	5	73	0.90	
T1c	14	1	13		
T2a	16	1	15		
T2b	30	3	27		
T2c	7	–	7		
T3	11	–	11		
Pre-radiation Gleason Grade	78	6	72	0.90	
6	50	3	47		
7	23	3	20		
8	3	–	3		
9	1	–	1		
10	1	–	1		
Adjuvant Hormonal Tx. to Rx.	17 (20%)	2 (25%)	15 (19.5%)	0.71	
*Median pre-SCA PSA (IQR)	4.7 (5.3)	3.75 (9.1)	4.7 (5.1)	0.49	
Gleason grade pre SCA	77	6	71	0.8	
6	25	2	23		
7	27	1	26		
8	15	2	13		
9	7	1	6		
10	3	–	3		
Time from Rx. To SCA (SD)	5.3 (2.7)	4.3 (1.6)	5.4 (2.8)	0.14	−0.91–3.11
BCR after SCA (%)	52 (61.1%)	8 (100%)	44 (57.1%)	0.018	
Time from SCA to BCR (SD)	3.1 (2.2)	3.4 (2.4)	3.17 (2.2)	0.88	−1.41–1.87
Metastatic disease (%)	24 (82.2%)	3 (37.5%)	21 (27.2%)	0.58	
CRPC (%)	37 (43.5%)	4 (50%)	33 (42.9%)	0.70	
% Dead	62 (72.9%)	4 (50%)	58 (75%)	0.12	
Time from SCA to Death (SD)	12.7 (4.4)	17.7 (7)	12.4 (4)	0.017	2.1–8.5

CI: confidence interval; SCA: Salvage Cryoablation; SD: standard deviation; IQR: interquartile range; PSA: Prostate Specific Antigen; Rx.: Radiation; BCR: Biochemical recurrence; CRPC: Castration Resistant Prostate Cancer.
*Non-parametric one-tailed Mann-Whitney test.

All patients had extensive calcifications, necessitating permanent suprapubic urinary drainage. If diagnosed with less extensive calcification involvement, a judicious attempt at complete transurethral resection may be worthwhile. Regrettably, we cannot report on quantitative measurements of the calcifications due to the descriptive nature of our study.

Conclusion

DC following SCA is an under-reported adverse effect having a significant impact on the patient's quality-of-life. As such, we encourage urologists to include this potential complication during patient counseling.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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