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Salvage cryoablation for local recurrence of prostatic cancer after curative therapy

Short title:

Cryoablation for prostate cancer recurrence

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Abstract

Purpose: The purpose of this study was to determine the efficacy of salvage cryotherapy for intra-prostatic and local extraprostatic recurrences after curative treatment of prostate adenocarcinoma.

Material and method: Twenty-eight patients (mean age, 69 ± 6 [SD] years; range: 51 – 82 years) treated with cryoablation for prostatic (n=21) or extraprostatic (n=7) recurrent prostate cancer after radiotherapy with or without associated prostatectomy were included. Technical success, complication and recurrences were reported. Biological recurrence was defined as an elevation ≥ 2 ng/mL of prostate specific antigen (PSA) serum level after the treatment.

Results: The mean follow-up was 18 months. Among the 21 patients with intraprostatic recurrence, 14 had successful cryotherapy with a mean decrease in serum prostate-specific antigen (PSA) levels of -5.7 ± 2.6 (SD) ng/mL (range: -2.1 to -16.9 ng/mL). Four patients (19%) had early progression and three (14%) patients had delayed biological recurrence (average time: 15 months). Among the 7 patients with extraprostatic recurrence, two had successful cryotherapy with a decrease in PSA serum level of -2.7 ± 1.6 (SD) ng/mL (range: -0.5 - -5.5 ng/mL) and 4/7 (57%) had early biological recurrence after cryotherapy that required androgen deprivation therapy, whereas one was lost to follow-up. No major complications were observed for both intra- and extraprostatic recurrence.

Conclusion: Salvage cryoablation of locally recurrent prostate cancer after curative treatment is feasible and safe when the half prostate is treated. It could delay initiation of androgen deprivation therapy in these patients.

Keywords: Salvage cryotherapy; Prostate cancer; Prostatic recurrence; Extraprostatic recurrence Percutaneous ablation.

Introduction

Prostate cancer is the most commonly diagnosed cancer in men worldwide, with 233000 cases and approximately 30000 deaths in the United States in 2014 [1]. For localized cancers, different treatments can be used including active surveillance and curative treatments, such as total prostatectomy, external beam radiotherapy and brachytherapy, with or without associated androgen deprivation therapy (ADT) [2].

After curative treatment, 20% to 50% of patients have biological recurrences, according to their initial prognostic factors [3, 4]. About 30% of these recurrences are local recurrences such as intra-prostatic or peri-prostatic pelvic recurrences that can be treated with a second local therapy [3, 4]. After prostatectomy, salvage radiotherapy is usually proposed, but after radiotherapy prostatectomy is highly complicated and associated with a high complication rate and re-irradiation is often impossible [5]. Local treatments as cryotherapy or high frequency focused ultrasound may have a role to play in this setting.

So far, cryotherapy has demonstrated interest in a variety of malignant tumors [6]. Salvage cryotherapy is also a possible treatment for biopsy-proven intraprostatic recurrence after external beam radiotherapy [7, 8]. It has proved safety, with approximately 50% of patients experiencing minor and transient complications such as perineal pain, hematuria or incontinence and less than 5% of patients experiencing major complications such as severe incontinence or pelvic fistulae formation that require surgical treatments [9, 10]. It is associated with a significantly lower rate of erectile dysfunction and a better cost-effectiveness ratio than palliative ADT [11,]. The biological recurrence-free survival after the treatment is up to 70% at 5 years and 30% at 10 years and is correlated with the initial Gleason score and the initial prostate-specific antigen (PSA) serum level [12, 13].

However, for local extraprostatic recurrences defined as focal pelvic or node recurrence without distant metastasis or disseminated disease, only few reports including a small number of patients for a short follow-up period have been published. For these indications, cryoablation therapy seems to be feasible and safe [14, 15].

The purpose of this study was to determine the efficacy of salvage cryotherapy for intra-prostatic and local extraprostatic recurrences after curative treatment of prostate adenocarcinoma.

Materials and methods

Patients

This single center, retrospective study was approved by our Institutional Review Board with a waiver of informed consent. From January 2011 to May 2016, all consecutive patients treated with cryotherapy for pathologically proven recurrences of prostate cancer with single intra-prostatic recurrence after radiotherapy or extraprostatic pelvic nodes after prostatectomy and radiotherapy without other distant metastases were included. Patients with more than one

metastasis or a PSA serum level >20 ng/mL were not considered for salvage therapy because these findings are associated with a high prevalence of systemic metastases. Patients were recruited after decision of a multidisciplinary staff. A total of 11 patients were excluded. The study population included 28 patients: 21 had prostatic recurrences and 7 had extraprostatic recurrences. Patient's characteristics are summarized in Table 1. The mean delay between initial treatment and recurrence was 7.5 years (range: 5.9 - 10.3 years) for prostatic recurrence and 9.9 years (range: 6.5-11.8 years) for extraprostatic recurrence. Flow chart of patients inclusion is presented in Figure 1.

Imaging evaluation

All patients had whole-body computed tomography (CT) examination and ^{18}F -fluorocholine positron emission tomography/CT (^{18}F -choline PET/CT) to exclude possible distant metastases. Recurrences were localized using MRI for intraprostatic recurrences and MRI and/or PET/CT for extraprostatic recurrences. Recurrences were suspected on the basis of Phoenix criteria: PSA serum level elevation (Nadir + 2ng/mL after radiotherapy or >0.2ng/mL after prostatectomy) during patient follow-up. Recurrences were documented with imaging either prostate MRI or ^{18}F -choline PET/CT examination performed by physicians with more than 15 years of experience in uroradiology) and confirmed with histopathological analysis of biopsy specimens. A multidisciplinary tumor board that included at least one urologist, one radiologist, one nuclear medicine physician, one pathologist and one radiation and medical oncologist validated each decision.

MRI examinations were performed using a Magnetom® 1.5-T scanner (Siemens Healthineers). Protocol included T2-weighted sequence, diffusion-weighted sequence obtained with b values of 50, 400 and 1200 sec/mm² and apparent diffusion coefficient map [16]. Then T1-weighted sequences were obtained before and after intravenous administration of gadoterate meglumine (Dotarem®, Guerbet).

^{18}F -choline PET/CT were performed using a Vereos® scanner (Philips Healthcare). Acquisition were performed 5 to 15 minutes after the injection of 2 to 4MBq/kg ^{18}F -choline.

Cryotherapy intervention

After multidisciplinary tumor board validation, all cryoablation interventions were performed during a short-time hospital stay of one to two nights using a third-generation cryo-technology system (Visual-ICE® System, Galil Medical Inc.). The number and type of

cryoprobes (17G diameter, IceRod® or IceSphere® needles) varied depending on the tumor size and location, as determined via the imaging workup. The same interventional radiologist (E. de K.) with an experience of more than 10 years in cryotherapy performed all procedures. For all interventions, surgical asepsis was applied. Interventions were performed under antibiotic prophylaxis and post-operative pain control protocols.

For prostatic recurrences, cryotherapies were performed in the operating room with patients under general anesthesia. Patients were installed in a gynecological position. Three to eight cryoprobes (median = 6) were positioned in the total prostate (n = 6 interventions) or in the hemiprostate (n = 15 interventions [left = 10 interventions, right = 5 interventions]) with a transperineal approach and ultrasound guidance by the operator. Maximum distance between cryoprobes was 0.5 cm as suggested previously [17]. To protect the rectum and the urinary sphincter, two thermocouples were placed by the radiologist, one at the level bladder neck and one in the Denonvilliers fascia or in the rectum wall. In addition, an urethral warmer was positioned endoscopically by the surgeon and its position was controlled by ultrasonography.

For extraprostatic recurrences, cryotherapies were performed in the CT room under local anesthesia using 10 to 20 mL of lidocaine 1% (Xylocaine, Aspen). The patient's position changed according to the target location. If needed because potential risk of bladder lesion or to facilitate the targeting procedure because of anatomical considerations, a bladder catheter could be inserted. Three to 4 cryoprobes (median = 3 cryoprobes) were positioned with a transparietal or transgluteal approach under CT guidance. For all interventions, treatment procedures included two 10-minutes freeze-thaw cycles [18]. Ice-balls were monitored with CT or ultrasound.

Targets volumes were defined by the preoperative multidisciplinary tumor board using preoperative MRI for prostatic recurrence and MRI or PET/CT for extraprostatic recurrence. Cryoprobes were placed with the same method as those described for prostate biopsy [19, 20].

Patients monitoring

After the treatment, patients monitoring was conducted using a standard protocol. All patients had a pelvic MRI, clinical evaluation and biological serum tests including PSA serum level at 7 days, 3 months, 1 year and then every year at least after cryotherapy. All observed adverse events were graded according to the society of international radiology as minor (A or B), major (C, D, E) or death (F grade) [21].

Evaluation criteria

The main outcome assessment was recurrence after salvage therapy, defined by the Phoenix criteria as an increase in PSA serum levels > 2 ng/mL compared with the nadir. Early recurrences were considered when PSA serum level increased in the first three months. Secondary outcome assessments were the complication rate and the associated required treatments. Technical success was considered when the procedure could be performed until the end with an ablation volume that included the whole targeted lesion with ablative margins equal or superior to those defined by the preoperative multidisciplinary tumor board evaluated on the first imaging examination performed immediately after the procedure [22].

Statistical analysis

Quantitative values were expressed as the median and range, and were compared using the nonparametric Mann-Whitney U-test. Qualitative values were expressed as percentages and were compared using Fisher's exact test. Disease-free survival (DFS) was estimated using the Kaplan-Meier method. The statistical significance for all tests was set at $P < 0.05$. SPSS® software version 20.0 (SPSS, IBM, USA) was used for the statistical analyses.

Results

Intraprostatic recurrence

Twenty-one patients with intraprostatic recurrence were treated. Six out of 21 patients (29%) had whole prostate cryotherapy, and 15/21 (71%) had hemi-ablative prostate therapy. All patients had technical success of the cryotherapy procedure with an iceball covering the whole tumor with a minimum of 5-mm margins observed during the procedure and considerable necrosis of the treated area without enhancement on T1-weighted imaging obtained after gadolinium-chelate injection on early MRI performed in the first 48 hours after cryotherapy (Fig. 2). Patient's characteristics are summarized in Table 2.

The mean follow-up was 19 ± 10 (SD) months (range: 8 – 40 months). Fourteen out of 21 patients (67%) had no recurrence during the follow-up, with a mean decrease in PSA levels of 5.7 ± 2.6 (SD) ng/mL [range: -2.1 - -16.9 ng/mL]. Four out of 21 patients (19%) had early progression during the first 3 months with a rapid increase in PSA serum level and required early ADT. Two of these patients developed early systemic progression with bone metastases and died 2 and 3 years after the salvage therapy. Three out of 21 patients (14%)

had delayed recurrences with a mean delay of 19 ± 8 (SD) months (range: 8 – 27 months). Mean PSA serum levels before cryotherapy were not significantly different in patients with recurrence (4.8 ± 2.4 [SD] ng/mL; range: 3.8 – 6.4 ng/mL) than in those without recurrence (7.0 ± 3.6 [SD] ng/mL; range: 5.4 – 8.5 ng/mL) ($P = 0.197$).

Five out of 21 patients (24%) had Grade 3 adverse events consisting in persistent incontinence requiring artificial urinary sphincter implantation in 3 patients, chronic pelvic pain requiring multimodal analgesic treatment in one patient and urethral stenosis requiring self-urethral catheterization in the remaining patient. Among these 5 patients, 4 (80%) had whole prostate ablative cryotherapy, and one a hemiprostate ablative focal cryotherapy. One other patient who had hemi-ablative focal therapy of the prostate had a minor complication consisting in a transient dysuria (Table 2).

Extraprostatic recurrences

Seven patients including 3 patients (43%) with pelvic lymph nodes recurrences and 4 patients (57%) with prostatectomy bed recurrences underwent cryotherapy for extraprostatic recurrence (Figs. 3, 4). Cryotherapy procedures were technically successful in all seven patients. Patient's characteristics are summarized in Table 3.

The mean follow-up was 20 ± 10 (SD) months (range: 12 – 32 months). Two patients had no recurrence during follow-up, with a median decrease in PSA serum levels of -6.31 ± 4.5 (SD) ng/mL (range: -1.84 - -10.85 ng/mL). One patient was lost to follow-up immediately after the procedure. Four patients developed recurrence during follow-up after cryotherapy, with a median delay of 15 months (range: 12 – 20 months); 3 were treated for prostatectomy bed recurrences, and one was treated for pelvic nodal recurrence.

No major complications (Grade 3 or more) were observed. Only one patient (1/7; 14%) who was treated for prerectal nodal recurrence had transient dysuria as a minor complication (grade 2).

Disease-free survival

Global DFS was 65.5% at 24 months for the overall population of 28 patient treated. The 2-years DFS was 72% for patients with treated intraprostatic recurrences and 43% those with for distant recurrences (Fig. 5).

Discussion

The results of our study show that for prostatic recurrences, salvage cryotherapy is feasible and safe when the hemiprostata is treated. Five patients (24%) had major complications including 4/6 (66%) patients who had cryotherapy of the whole prostate and 1/15 (7%) patient who underwent cryotherapy of the hemiprostata. These results are consistent with those of Pisters et al. who found a 44% biological recurrence-free survival rate at 5 years in a series of 279 patients; only 60% of grade 3-4 adverse events occurred in patients who underwent whole prostate cryotherapy [7]. A recent large meta-analysis including 3995 patients confirmed these results [23].

The high rate of grade 3 or 4 complication when the whole prostate is treated with cryotherapy has already been reported and should lead interventional radiologist or urologist to avoid these techniques [7]. Physiopathology of these complications has not been fully elucidated yet but all studies confirmed that rates of serious complications are lower when only a hemiprostata is treated. This observation suggests that when a bilateral prostatic cryotherapy is required, treatment should be performed during two different sessions [7, 23].

In our study, four patients had early recurrences; two of them had early bone metastases. This corresponds to initial poor selection of patients with pre-existing metastasis. It is important to stress that patients must be carefully selected in order to improve the long-term results of salvage therapy and to propose the best care to these patients. The classical indications for a local salvage treatment are biopsy-proven recurrences with a PSA serum level < 10 ng/mL, a negative 99m Technetium bone scintigraphy and no soft-tissue metastasis present on CT, MRI or PET/CT examination [24].

For extraprostatic recurrences, salvage cryotherapy proved to be feasible with only one minor and transient complication occurring in one of 7 patients in our study. However, most of the patients had tumor relapse within a short time. ADT was delayed with a median of 15 months [12 – 20 months]. This suggests that the single recurrence target identified by morphological and functional imaging methods reflects the beginning of a systemic metastatic dissemination. Considering these findings, salvage cryotherapy can be considered to delay the introduction of ADT, which often results in weight gain, metabolic syndrome, depression, osteoporosis and erectile dysfunction and a potential future hormonal resistance [25]. This treatment option should be discussed with each patient individually, and the use of this technique requires clear patient information. To our knowledge, only a few studies about

focal therapy for extraprostatic recurrence of prostate adenocarcinoma, with a limited number of patients have been published. Cornelis et al. performed a feasibility study using a transgluteal CT-guided cryoablation for two patients with pelvic recurrence [14]. No complications were found, but one patient had recurrence 3 months after the treatment. Erie et al. included 16 patients with oligometastatic recurrence of prostate cancer treated with percutaneous cryoablation for bone or nodes metastases [15].

Compared with other salvage treatments for prostatic recurrences after external beam radiation therapy, high frequency focused ultrasound yields similar results to cryotherapy in terms of oncological control but seems to cause less minor complications than cryotherapy [26]. On the other hand, salvage robotic prostatectomy is associated with more complications than cryotherapy, and particularly incontinence [25, 27].

Our study has several limitations. First, the single-center and retrospective design may have induced a recruitment bias and limits the conclusion. In addition, only 21 patients with prostatic recurrences and 7 with extraprostatic recurrences were included. Then, the median follow-up time was quite short, particularly for patients with extraprostatic recurrences. However, the extraprostatic recurrence rate during follow-up in our study was similar to that in other studies [15]. Finally, no MRI-guidance system was used to improve lesion targeting [28].

In conclusion, for prostatic recurrences after curative external radiotherapy with or without associated prostatectomy, salvage cryotherapy was confirmed to be a feasible. It seems to be a safe and efficient method that could be a promising method to delay ADT when the hemiprostate was treated in well-selected patients. A high rate of complications occurs when the whole prostate is treated. Cryotherapy for extraprostatic recurrences was also a feasible technique that allowed delayed initiation of ADT.

Funding

The study did not receive any external source of founding.

Conflicts of interest

The authors declare that they have no conflict of interest in relation with this study.

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Figure legends

Figure 1. Diagram show flowchart of inclusion of patients.

Figure 2. Biopsy-proven right hemiprostate recurrence in a 61-year-old man treated with external radiotherapy for a T2aN0M0 prostate adenocarcinoma. The patient's initial Gleason score was 6 (3+3), and his PSA serum level before salvage therapy was 8.9 ng/mL. After cryotherapy, the patient had a decrease of PSA serum level of 0.49 ng/mL. He had no systemic recurrence after 30 months of follow-up. A: Diffusion-weighted MR image with a high b-value ($b=1000\text{s/mm}^2$) in the axial plane shows diffusion restriction in the right hemiprostate corresponding to the recurrence site (arrow). B: Transrectal ultrasound image obtained during cryotherapy in the operating room shows 6 cryoprobes in the right hemiprostate (arrows). C: T1-weighted MR image in the axial plane obtained after intravenous administration of gadoterate meglumine (Dotarem®, Guerbet) 24 hours after cryotherapy shows unenhanced treated zone in the right hemiprostate (arrow).

Figure 3. Biopsy-proven extraprostatic left iliac lymph node recurrence in a 78-year-old patient treated with total prostatectomy and adjuvant radiotherapy 7 years previously for a T2aN0M0 prostate adenocarcinoma. The patient's initial Gleason score was 8 (4+4), and his PSA serum level before salvage therapy was 3.9 ng/mL. After cryotherapy, the patient had undetectable PSA serum level. He had systemic recurrence and required androgen deprivation therapy 14 months after salvage cryotherapy. A: 18-fluorodeoxyglucose PET/CT image in the axial plane shows hypermetabolism of a left iliac lymph node (arrow). B: Unenhanced CT image obtained in the axial plane shows 2 cryoprobes in the left iliac lymph node with a posterior paravertebral approach and the corresponding hypodense ice ball.

Figure 4. Biopsy-proven extraprostatic prostatectomy bed recurrence in a 68-year-old patient treated with total prostatectomy and adjuvant radiotherapy 11 years previously for a T3aN0M0 prostate adenocarcinoma. His initial Gleason score was 7 (4+3), and his PSA serum level before salvage therapy was 2.4 ng/mL. After cryotherapy, the patient had a serum PSA level of 1.9 ng/mL. He had systemic recurrence and required androgen deprivation therapy 5 months after salvage cryotherapy. A: 18-fluorodeoxyglucose PET/CT image in the axial plane shows hypermetabolism of the right side of the prostatectomy bed (arrow). B: Unenhanced CT image in the axial plane shows 2 cryoprobes in the right side of the prostatectomy bed with a transgluteal approach and the corresponding hypoattenuating ice ball. C: Unenhanced CT image in the sagittal plane shows 3 cryoprobes in the right side of the prostatectomy bed with a transgluteal approach and the corresponding hypodense ice ball.

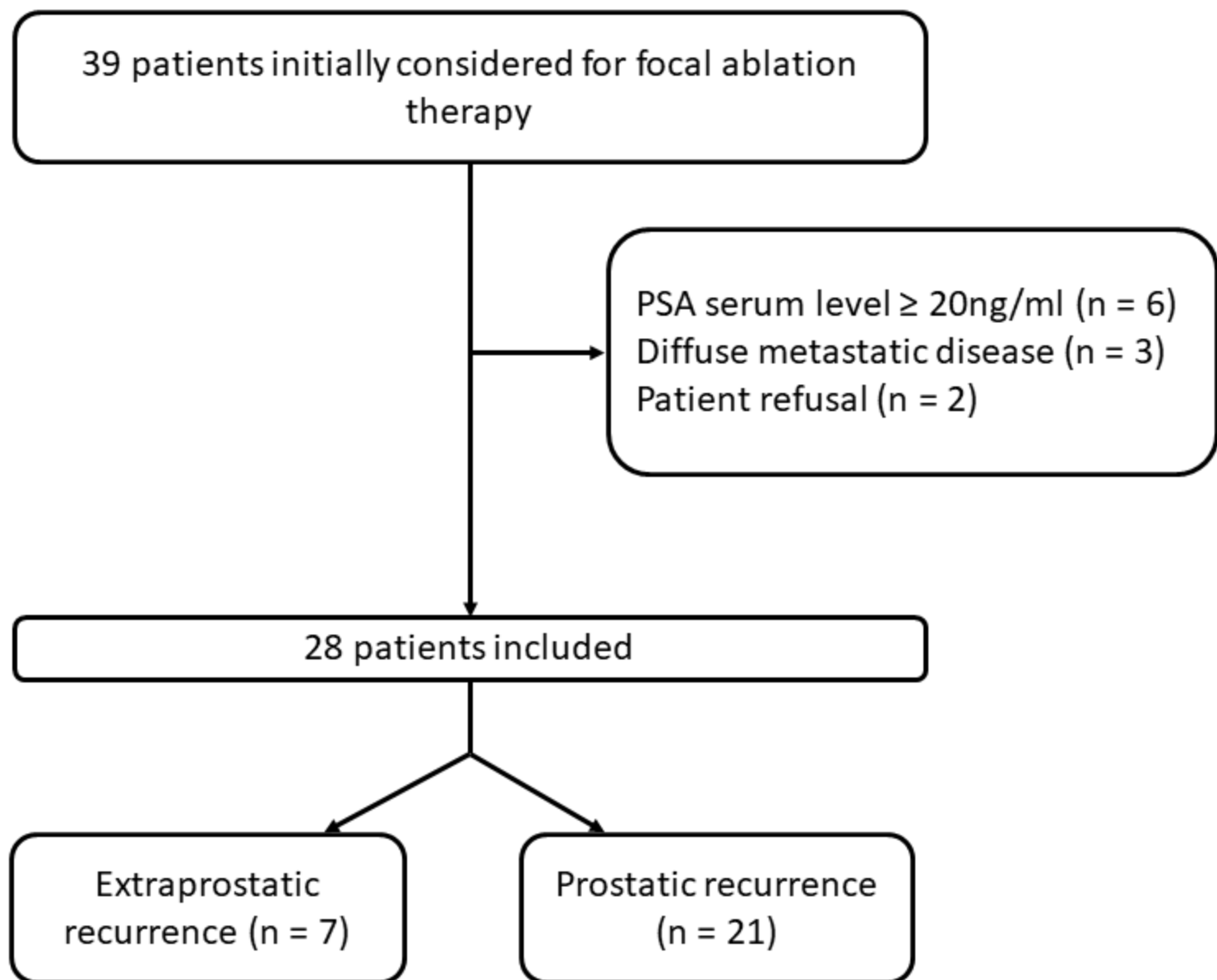
Figure 5. Survival curves for the disease-free survival after cryotherapy. A: Graph shows overall disease-free survival (DFS) for the global population study regardless recurrence site. Global DFS was 65.5% at 24 months for the overall population of 28 patient treated. B: Graph shows DFS according to cryotherapy site. The 2-year DFS was 72% for

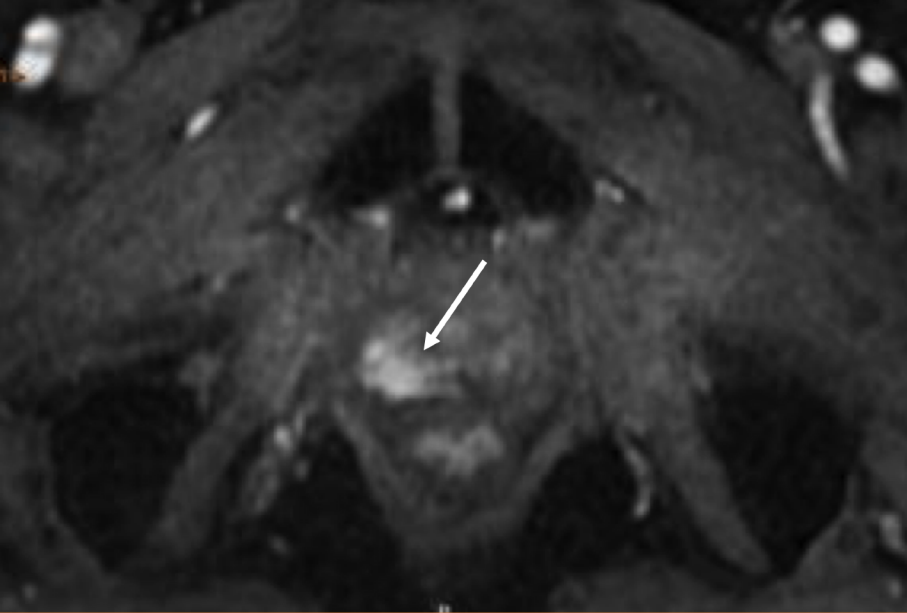
prostate treated recurrences and 43% for distant recurrences (seminal vesicles or lymph nodes).

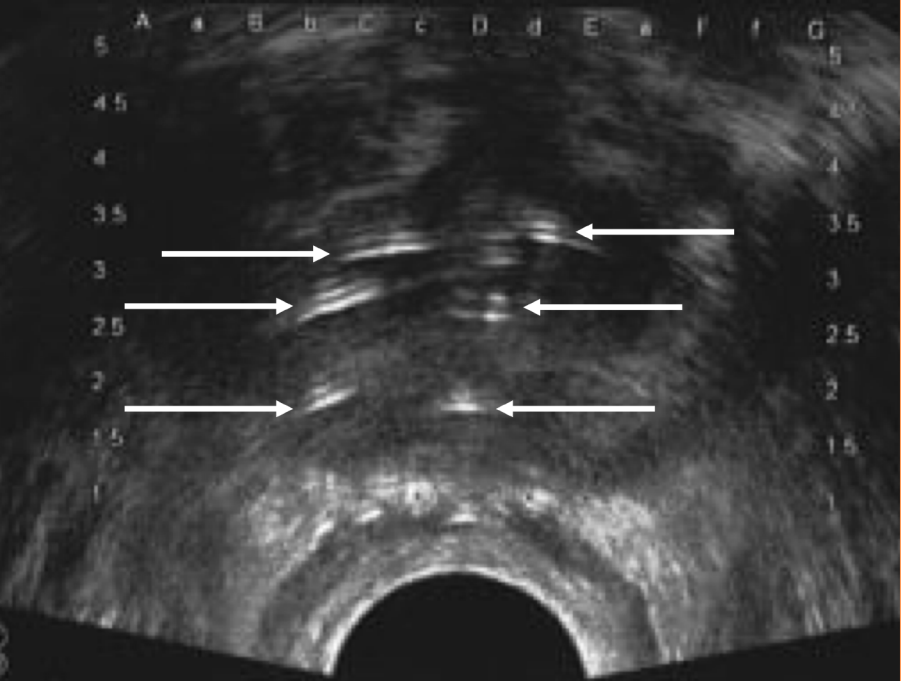
Table 1. Initial characteristics in 28 patients with recurrence of prostatic cancer.

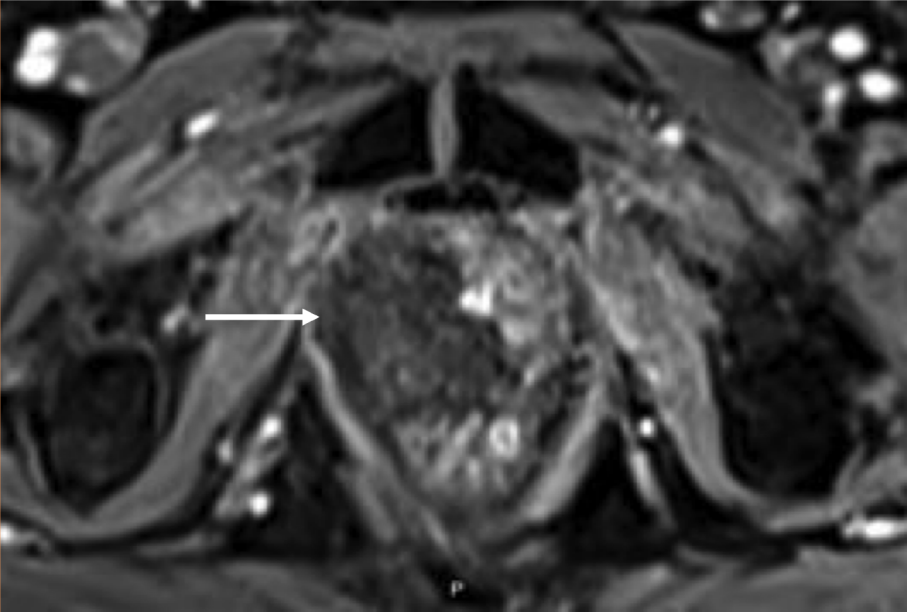
Table 2. Characteristics and follow-up of 21 patients treated with cryotherapy for intraprostatic recurrence after curative radiotherapy.

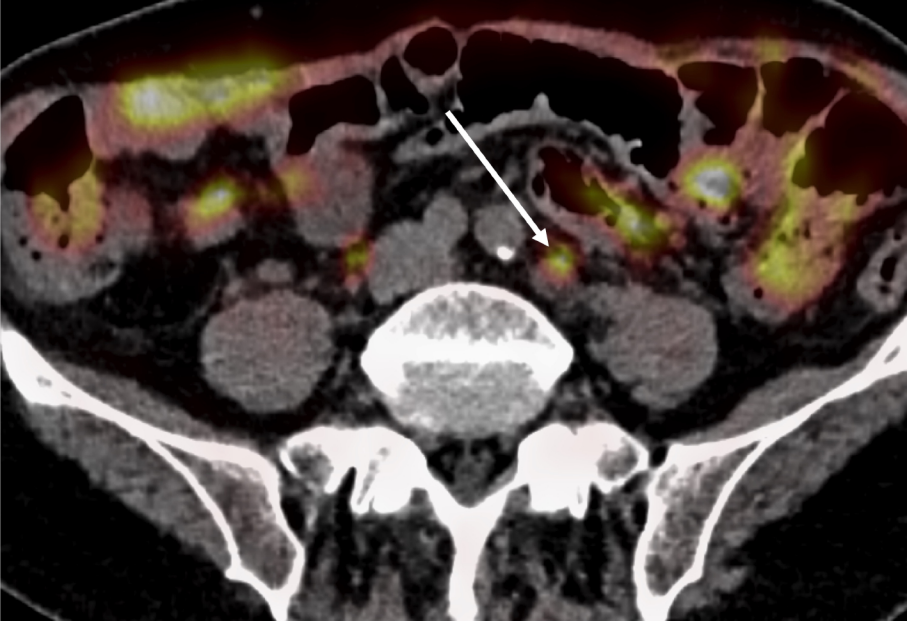
Table 3. Characteristics and follow-up of 7 patients treated with cryotherapy for extraprostatic recurrence of prostatic cancer after prostatectomy.

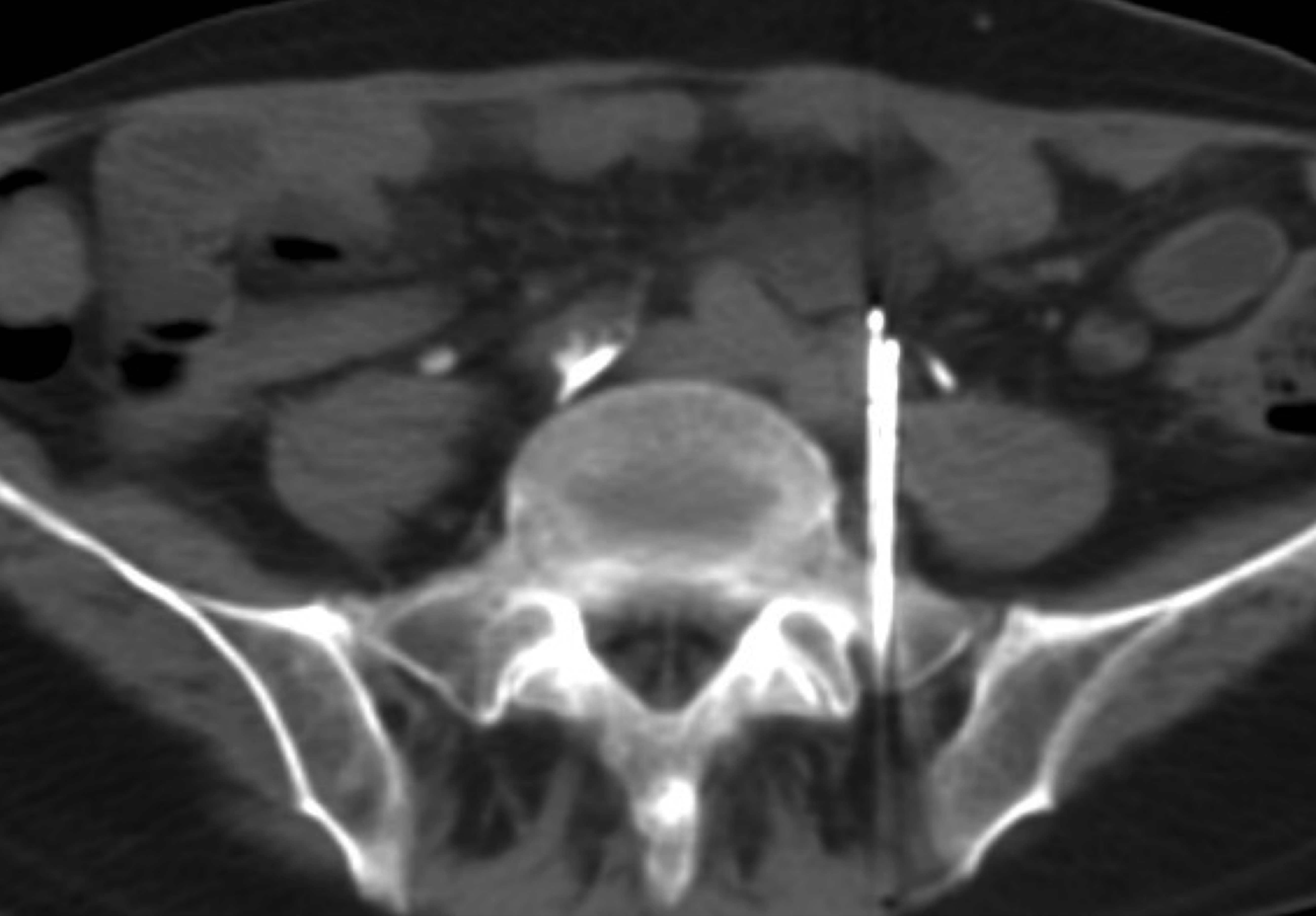


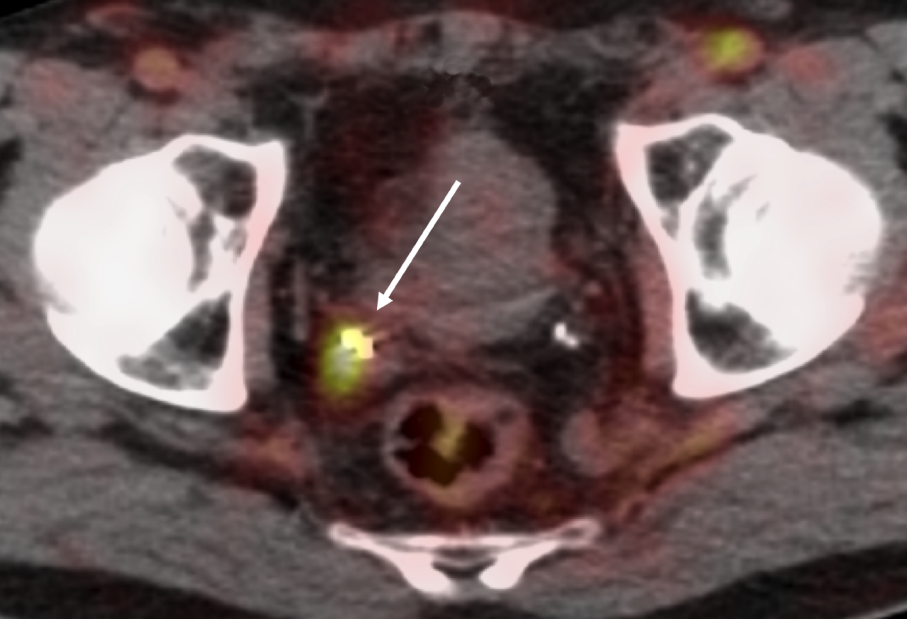


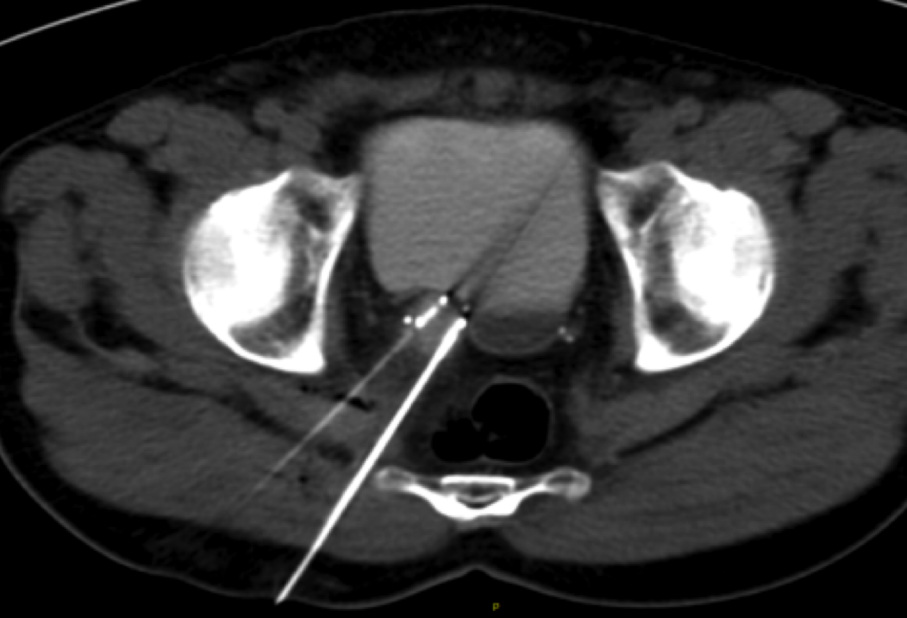


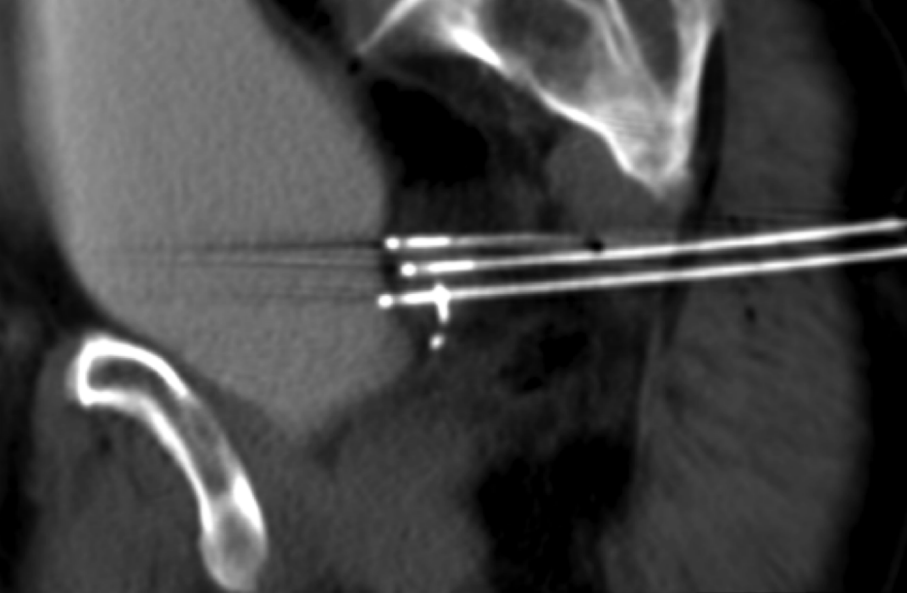




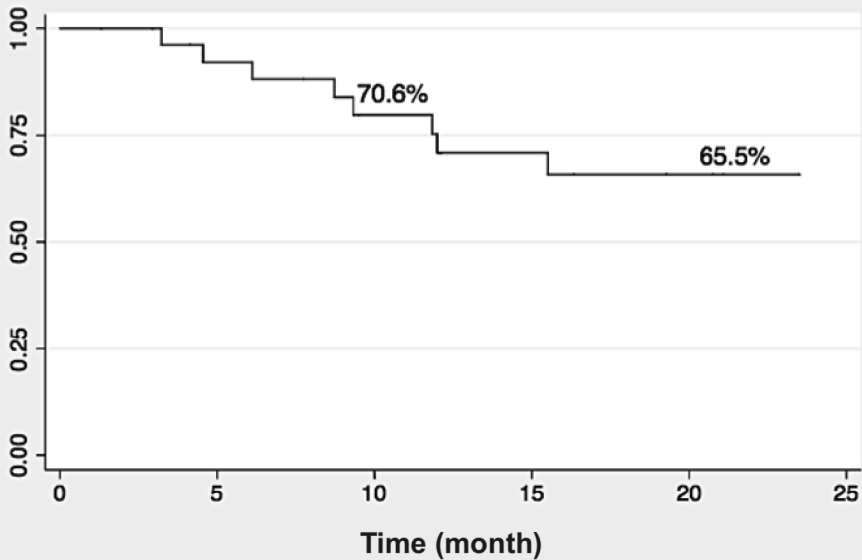




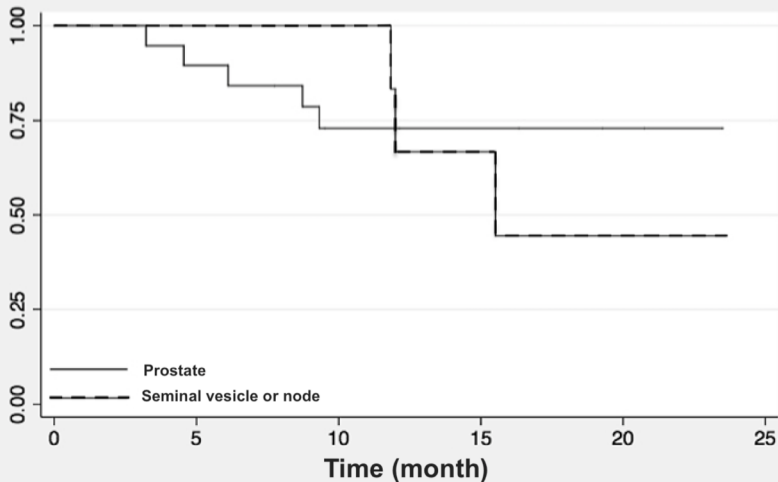




Disease-free survival



DFS according to cryotherapy location



Groups		Prostatic recurrence	Extraprostatic recurrence
Number (n)		21	7
Age (years)		68 ± 5.8 [51 – 82]	70 ± 4.0 [64 – 78]
Initial PSA serum level (ng/mL)		11.5 ± 7.5 [2.6 – 50.0]	17.3 ± 14.3 [5.8 – 53.4]
Initial Gleason score			
	6	9 (43%)	2 (29%)
	7	11 (52%)	4 (57%)
	8	1 (5%)	1 (14%)
Previous treatment (n)			
	<i>External radiotherapy</i>	21 (100%)	7 (100%)
	<i>Prostatectomy</i>	0 (0%)	7 (100%)
	<i>Brachytherapy</i>	2 (10%)	0 (0%)
	<i>Chemotherapy</i>	0 (0%)	0 (0%)
	<i>Hormonotherapy</i>	6 (29%)	4 (57%)
Time from initial diagnosis to cryotherapy (years)		8.3 ± 2.7 [1.5 – 14.8]	9.1 ± 2.7 [3.1-12.0]
PSA serum level at recurrence (ng/mL)		6.3 ± 2.4 [3.0 – 18]	4.3 ± 2.6 [0.9 – 11.0]
Recurrence location (n)			
	<i>Prostate</i>	21 (100%)	0 (0%)
	<i>Prostatectomy bed</i>	0 (0%)	4 (57%)
	<i>Pelvic lymph nodes</i>	0 (0%)	3 (43%)

Quantitative variables are expressed as means ± standard deviations. Numbers in brackets are ranges.

Qualitative variables are expressed as raw numbers. Numbers in parentheses are percentages.

PSA indicates prostatic specific antigen

N°	Delay in recurrence (month)	PSA level before cryotherapy (ng/mL)	Treated zone	Nadir PSA level (ng/mL)	Complication	Recurrence	Death	Follow-up (month)
1	18	8.54	Hemiprostate	0.69	No	No	No	12
2	48	18	Hemiprostate	1.1	No	No	No	15
3	79	4.49	Hemiprostate	0.39	No		No	30
4	77	9.3	Hemiprostate	12.69	No	Yes	No	9
5	177	4.25	Hemiprostate	0.03	No	No	No	18
6	79	3.91	Hemiprostate	4.3	No	Yes	No	6
7	111	5.1	Hemiprostate	0.27	No	No	No	5
8	71	5.36	Hemiprostate	3.29	Transient dysuria	Yes	No	19
9	134	8.99	Hemiprostate	0.57	No	No	No	3
10	129	4.35	Hemiprostate	0.32	Transient dysuria	No	No	30
11	116	6.74	Hemiprostate	0.02	Transient dysuria	No	No	24
12	110	8.6	Hemiprostate	1.17	No	Yes	No	9
13	152	5.38	Hemiprostate	7.18	No	Yes	No	1
14	137	3.02	Hemiprostate	0.01	Urethral stenosis		No	16
15	72	8.47	Hemiprostate	57	No	Yes	Yes	29
16	162	3.5	Whole prostate	0.03	Transient incontinence	No	No	24
17	92	3.6	Whole prostate	0.01	Persistent incontinence	No	No	38
18	32	7	Whole prostate	1200	No	Yes	Yes	41
19	106	5.27	Whole prostate	0.12	No	No	No	8
20	85	3.5	Whole prostate	0.39	Chronic pelvic pain	No	No	29
21	102	5.3	Whole prostate	2.98	Urinary frequency	No	No	33

Numbers in bold are early recurrences.

N°	Delay in recurrence (months)	PSA level before cryotherapy (ng/mL)	Treated area	Nadir PSA level (ng/mL)	Complication	Recurrence	Follow-up (month)
1	99	3.9	2 iliac lymph nodes	0.03	No	Yes	13
2	135	2.1	1 prerectal lymph node	0.26	No	No	14
3	144	2.4	Right PB	2.04	No	Yes	18
4	79	2.12	Right PB	0.43	No	Yes	32
5	37	0.95	Right PB	0.48	Transient dysuria	Yes	34
6	121	5.54	Left PB	N.A.	N.A.	N.A.	0
7	152	10.9	1 pelvic node	0.05	No	No	12

PB indicates prostatectomy bed. N.A. indicates not available.