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TREATMENT OF ORGAN CONFINED PROSTATE CANCER WITH THIRD GENERATION CRYOSURGERY: PRELIMINARY MULTICENTER EXPERIENCE

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ABSTRACT

Purpose: Cryosurgical ablation of the prostate is 1 approach to the treatment of localized prostate cancer. Third generation cryosurgery uses gas driven probes that allow for a decrease in probe diameter to 17 gauge (1.5 mm). The safety, morbidity and preliminary prostate specific antigen (PSA) results of 122 cases are reported.

Materials and Methods: A total of 106 patients have undergone percutaneous cryosurgery using a brachytherapy template with at least 12 months of PSA followup. Immediate and delayed morbidities were evaluated. PSA results at 3 and 12 months were recorded, and failure was defined as the inability to reach a nadir of 0.4 ng/ml or less.

Results: Complications in patients undergoing primary cryosurgery included tissue sloughing (5%), incontinence (pads, 3%), urge incontinence/no pads (5%), transient urinary retention (3.3%) and rectal discomfort (2.6%). There were no cases of fistulas or infections. Postoperative impotence was 87% in previously potent patients. For patients who underwent salvage cryosurgery there were no fistulas reported and 2 (11%) patients required pads after salvage cryosurgery. A total of 96 (81%) patients achieved a PSA nadir of 0.4 ng/ml or less at 3 months of followup, while 79 of 106 (75%) remained free from biochemical recurrence at 12 months. A total of 42 (78%) low risk patients (Gleason score 7 or less and PSA 10 or less) remained with a PSA of 0.4 ng/ml or less at 12 months of followup, compared to 37 (71%) high risk patients. All patients were discharged within 24 hours.

Conclusions: After a followup of 1 year 3rd generation cryosurgery appears to be well tolerated and minimally invasive. The use of ultrathin needles through a brachytherapy template allows for a simple percutaneous procedure and a relatively short learning curve. A prospective multicenter trial is ongoing to determine the long-term efficacy of this technique.

KEY WORDS: cryosurgery, prostatic neoplasms, salvage therapy

The main treatment options for clinically localized prostate cancer currently consist of surgical extirpation and radiation therapy (external beam radiation therapy [EBRT] and/or brachytherapy). Cryosurgery has reemerged as an evolving technology and a minimally invasive treatment option. In 1996 the American Urological Association recognized cryoablation as a therapeutic option for prostate cancer in its position statement and removed the "investigational" label from this procedure.

First generation cryosurgery was performed in the 1960s and 1970s without transrectal ultrasound (TRUS) guidance or urethral warmers. Complications were common and often significant, and included incontinence, sloughing and rectourethral fistulas. These complications were due to the lack of accurate means of monitoring the freezing process. Second generation cryosurgery saw the development and implementation of TRUS[1] and urethral warmers,[2,3] which significantly decreased the number of complications. Ultrasound guidance allowed for accurate placement of probes, and real-time monitoring and control of freezing. In addition, urethral warmers significantly decreased the risk of urethral sloughing.

The evolution of 3rd generation cryosurgery includes 2 more advances. Gas driven probes were first described in 1997 by Wong et al[4] followed shortly by Chin et al.[5] This system signaled the transition from liquid nitrogen to gas driven probes in which pressurized gas can be used to freeze (argon gas) and thaw (helium gas) the organ according to the Joule-Thompson effect, in which different gasses undergo

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unique temperature changes when depressurized according to unique gas coefficients. This transition from liquid to gas permits the use of smaller diameter probes. This report presents a new technique using 3rd generation cryosurgery probes or "cryoneedles" that allow for direct transperineal probe placement through a brachytherapy-like template, without the use of tract dilation and insertion kits.

Potential indications for using this emerging technology include patients with clinically organ confined prostate cancer who choose cryotherapy or patients considered higher risk for radical prostatectomy (due to medical/anesthesia considerations), and patients in whom primary radiation therapy (XRT) has failed.[6] This report details the advancement of this minimally invasive technique, and summarizes preliminary prostate specific antigen (PSA) results and complication rates from a multi-institutional experience.

MATERIALS AND METHODS

Patient selection. A 17 gauge cryoneedle (Galil Medical, Westbury, New York) and a brachytherapy template were used, and 122 patients underwent cryoablation of the prostate gland between 2000 and 2002 at 8 institutions. All patients had biopsy proven prostate cancer. Preoperative Gleason scores, gland size and PSA were recorded. Mean patient age was 69.7 years (range 53 to 85) and median age was 70. Tumor staging was performed using digital rectal examination and transrectal ultrasound imaging, and classified according to the 1997 TNM staging system.[7]

Technique. The technique has been previously reported.[8] Briefly, the patients underwent a bowel preparation the evening before surgery. The patients were put under general or regional anesthesia and then placed in an exaggerated lithotomy position. Intravenous antibiotics were administered and a 17 gauge brachytherapy template was placed over the perineum. A multifrequency biplanar TRUS probe was used to image the prostate and measure its dimensions. The 17 gauge cryoneedles (1.47 mm in diameter) were then inserted under TRUS guidance, each spaced approximately 1 cm apart. Unlike previously reported techniques, cannulas and dilators were not necessary to create tracts for cryoneedle insertion. Depending on the size of the prostate, approximately 12 to 15 needles were placed to outline the shape of the prostate. Figure 1 illustrates typical cryoneedle placement.

Depending on the preference and experience of the surgeon, up to 5 thermocouples were placed at mid gland, level of external sphincter, left neurovascular bundle, right neurovascular bundle and Denonvilliers' fascia. Thermosensors at the level of the external sphincter and in Denonvilliers' fascia were used to minimize the risk of incontinence or rectourethral fistula. Thermosensors in the mid gland and neurovascular bundles ensured that the required temperature of −40C was reached for effective cell killing. Figure 2 demonstrates a schematic of thermosensor placement at the level of the external sphincter and in Denonvilliers' fascia.

Once the cryoneedles were placed a flexible cystoscopy was performed to ensure that none of the needles had inadvertently pierced the urethra. At this time, depending on surgeon preference, a suprapubic catheter was placed under direct visualization. Some surgeons have converted simply to leaving an indwelling Foley catheter for 3 to 5 days postoperatively. With the flexible cystoscope still in the urethra, a 0.038 inch guidewire was then inserted through the scope and into the bladder. After removal of the scope the urethral warmer was placed over the 0.038 inch guidewire.

Two freeze-thaw cycles were performed under TRUS guidance. In prostates longer than 27 mm in length a pullback procedure was performed to cover the apex since that is the length of the effectively cytotoxic ice ball isotherm. The cryoneedles were pulled back in between the 2nd and 3rd freethaw cycles to freeze the apical portion of prostate not originally frozen by the initial 2 cycles. As a result prostates longer than 27 mm underwent a total of 4 free-thaw cycles during which the prostate gland was completely encompassed in an ice ball. After completion of the freeze-thaw cycles the urethral warmer was left in place for up to 5 minutes to minimize the risk of urethral sloughing, which could produce urinary retention and irritative voiding symptoms.

The cryoneedles were then removed and gentle pressure was applied to the perineum for 2 to 5 minutes to minimize bleeding. No sutures were necessary to close the tracts. After completion of the procedure a Foley catheter was inserted or the suprapubic tube was left open. Patients were generally discharged the following day.

Results assessment. All data were prospectively collected. Patients were followed with clinical examinations and serial PSA measurements at 3-month intervals. Patient reported questionnaires regarding complications and symptoms were collected in a prospective manner as well. Complications evaluated included urethral sloughing, urinary retention, urge incontinence (no pads, but irritative symptoms), stress incontinence (pads), penile paresthesia, pelvic pain, scrotal

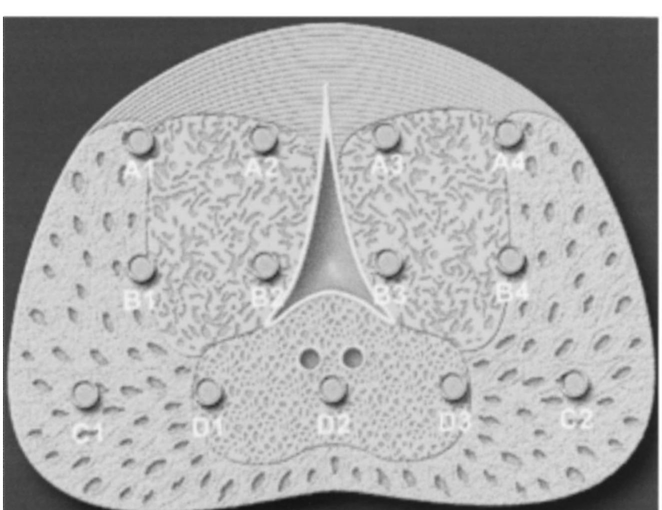

FIG. 1. Schematic diagram of cryoneedle placement in prostate (axial view).

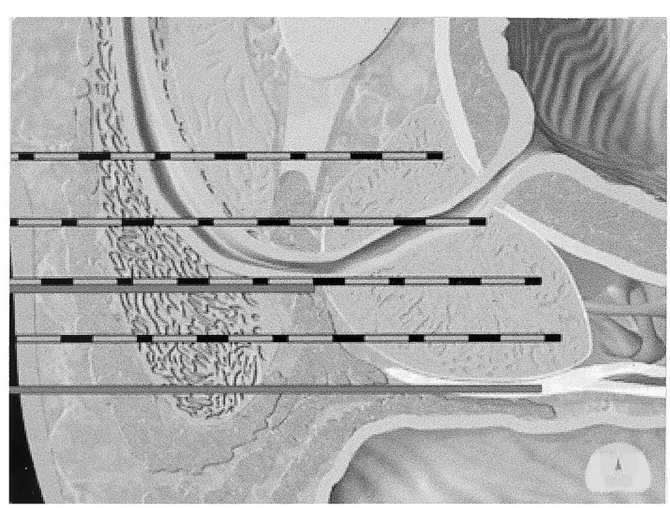

FIG. 2. Sagittal view of prostate with 4 rows of cryoneedles and 2 thermosensors. One thermosensor is at level of external sphincter while other is in Denonvilliers' fascia.

swelling and impotence. Biochemical assessment for efficacy was measured with PSA values at 3, 6, 9 and 12 months after treatment. Failure was defined as an inability to achieve and maintain a PSA value of less than or equal to 0.4 ng/ml. Followup biopsies were not routinely performed.

Statistical analysis. Patients were stratified according to preoperative PSA (10 or less versus greater than 10), Gleason score (6 or less versus greater than 6), and low risk versus high risk groups. Low risk patients were defined as those with Gleason scores of 6 or less, PSA 10 or less and clinical stage T1 or T2 disease. All remaining patients were stratified as high risk. Patients were also compared based on whether they had received previous XRT. All statistical analyses were conducted using Statistica version 6.1 (StatSoft, Tulsa, Oklahoma).

RESULTS

Patient characteristics. Table 1 summarizes the preoperative characteristics of the study population. Mean patient age was 69.7 years (range 53 to 85). A total of 75 (61%) of the patients had a preoperative Gleason score of 6 or less, 29 (24%) had a Gleason score of 7, while the remaining 18 (15%) had Gleason scores of 8 to 10. A total of 91 (75%) patients had a preoperative PSA of 10 ng/ml or less while the remaining patients had a PSA greater than 10 ng/ml. The study population was almost evenly distributed into low risk (48%) and high risk (52%) groups. Salvage cryotherapy was performed on 18 (15%) patients. Approximately one-third of the patients received preoperative hormone therapy. Depending on the preference of the surgeon some patients received hormones for downsizing purposes, while others were started on hormones due to high risk features including high Gleason scores and/or PSA levels greater than 10 ng/ml. Hormone therapy was stopped after completion of the procedure. All patients except 2 were discharged by the following day.

Complications. Morbidities associated with cryosurgery are summarized in table 2. Urethral sloughing was seen in 2 (11%) patients who had previously received XRT compared to 4.9% in patients undergoing primary cryotherapy. Urethral sloughing led to irritative voiding symptoms and, rarely, to urinary retention. The incontinence rate in patients undergoing salvage cryotherapy was 17% (3 patients), with 2 (11%) of these patients requiring pads. The remaining patient complained of severe urge incontinence/irritative symptoms. Three (3%) patients required pads for incontinence after undergoing primary cryosurgery. Overall 5 (4.2%) patients reported that they were using pads after cryosurgery while another 6 (5.1%) complained of urge incontinence. Impotence rates were 86% (salvage cryotherapy) and 87% (primary cryotherapy) in patients who were previously potent, while the rates of penile paresthesia, pelvic pain and scrotal swelling were low, all of the latter 3 complications resolved with conservative management. Finally, there were no urethrorectal fistulas or strictures.

PSA followup. At 3-month followup 118 patients had a PSA value available for evaluation. A total of 96 (81%) patients had a PSA at or below 0.4 ng/ml at 3 months, while the biochemical recurrence-free survival (BRFS) was 75% (79 of 106) at 12 months (table 3). For patients with a preoperative Gleason score of 6 or less, the BRFS rates were 84% and 74% at 3 and 12 months, respectively. For patients with a preoperative PSA of 10 ng/ml or less the numbers were 85% (3 months) and 76% (12 months), respectively. By comparison the rates for patients with a preoperative PSA greater than 10 ng/ml were 69% (3 months) and 71% (12 months).

Of 58 low risk patients (Gleason 6 or less, PSA 10 or less, clinical T1 or T2) 50 (86%) were able to achieve a PSA value of 0.4 ng/ml or less while the BRFS rate was 78% at 12 months (table 3). In contrast, the rates for high risk patients were 77% (3 months) and 71% (12 months), respectively. Thirteen (77%) patients with a history of radiation therapy (either brachytherapy and/or EBRT) remained biochemically free of disease at 12 months compared to 66 (74%) patients who underwent primary cryosurgery.

DISCUSSION

Optimal management of prostate cancer remains a subject of debate. Given the high incidence of the disease and the morbidities associated with standard options, physicians and patients continue to be interested in minimally invasive options. Preliminary data and complications using a third generation cryosurgery technique are presented.

Briefly, cryosurgery uses freezing techniques to induce cell death by a variety of mechanisms. Direct cellular injury occurs when cell metabolism fails as temperatures decrease. As temperatures decrease below −20C water in the extracellular environment crystallizes into ice. This process results in the withdrawal of water from the system, creating a hyperosmotic extracellular environment. As water is drawn out of the cells, denaturation and electrolyte imbalances occur.[9] During thawing ice crystals fuse to form larger crystals

TABLE 1. *Patient characteristics*

No. pts	122	
Mean/median age (range)	69.7/70	(53–85)
No. Gleason (%):		
2–5	19	(15.6)
6	56	(45.9)
7	29	(23.8)
8–10	18	(14.7)
No. PSA (%):		
10 or Less	91	(74.6)
Greater than 10	31	(25.4)
No. T stage (%):		
T1	53	(43.8)
T2	63	(52.1)
T3	5	(4.1)
No. risk (%):*		
Low	59	(48.4)
High	63	(51.6)
Mean/median prostate size (SD)	28.5/28.05	(9.5)
No. prior XRT (%)	18	(14.8)
No. prior hormone therapy (%)	45	(36.9)
Mean/median probes used (SD)	12.7/13	(2.0)

* Gleason less than 7, PSA 10 or less, clinical T1 or T2.

TABLE 2. *Postoperative complications*

Complication	No./Total No. (%)		
	XRT	No XRT	Overall
Urethral sloughing	2/18 (11)	5/102 (5)	7/120 (5.8)
Urge incontinence (no pads)	1/18 (5.6)	5/99 (5)	6/117 (5.1)
Incontinence (pads)	2/18 (11)	3/99 (3)	5/117 (4.3)
Penile tingling/numbness	1/17 (5.9)	2/100 (2)	3/117 (2.6)
Impotence	12/14 (86)	83/95 (87)	95/109 (87)
Pelvic pain	1/18 (5.6)	6/100 (6)	7/118 (5.9)
Scrotal swelling	2/18 (11)	5/101 (5)	7/119 (5.9)

TABLE 3. *PSA 0.4 ng/ml or less at 3 and 12 months*

Category	No./Total No. (%)	
	3 Mos	12 Mos
Gleason:		
Less than 7	61/73 (84)	50/68 (74)
7 or Greater	35/45 (78)	29/38 (76)
PSA:		
10 or Less	76/89 (85)	62/82 (76)
Greater than 10	20/29 (69)	17/24 (71)
Risk:		
Low	50/58 (86)	42/54 (78)
High	46/60 (77)	37/52 (71)
XRT:		
No	82/101 (81)	66/89 (74)
Yes	14/17 (82)	13/17 (77)
Overall	96/118 (81)	79/106 (75)

which eventually disrupt the cell membrane. After an initial period of vasoconstriction secondary to decreased temperatures, vasodilation, increased cellular permeability and then edema follow as temperatures increase. Endothelial damage leads to platelet aggregation and microthrombi formation, which leads to stagnation of circulation.[9] In addition, freezing is believed to induce apoptosis and possibly work via activation of the immune system.[9]

The technique described in this report incorporates recent advances in cryosurgery which allow for a safe, minimally invasive option for the treatment of prostate cancer. While the use of TRUS guidance and urethral warmers has significantly decreased complication rates associated with cryosurgery, the development of 17 gauge (1.5 mm) "cryoneedles" has eliminated the need for serial dilation and tract formation for placement of older generation cryoprobes (3.5 to 5.5 mm). This development has eliminated the need for closing the tracts with suture material and has significantly minimized scrotal swelling and perineal ecchymosis. One series that used the larger probes reported a 10.5% rate of scrotal swelling.[6] In addition, the smaller diameter cryoneedles allow for more needles to be placed (mean 12.7) compared to older generation probes (3 to 7 probes). As a result, more precise contouring of the prostatic ice ball is obtained in our opinion.

Biochemical freedom from recurrence was defined as a PSA of 0.4 ng/ml or less for this study cohort after a review of radiation oncology literature revealed a wide range of "acceptable" PSA nadir values (0.2 to 4.0 ng/ml).[10–14] This wide range is seen because the prostate is not removed and residual benign prostate tissue may release PSA. Recent literature has suggested that patients who reached a PSA nadir of 0.4 ng/ml or less have the highest probability of cure after XRT therapy.[12,13] As a result the same value was chosen to define biochemical failure after cryosurgery.

Long-term PSA followup and survival data are needed before any conclusions about the efficacy of 3rd generation cryosurgery can be drawn. With that said the BRFS rate at 12 months was 76% for patients with a preoperative PSA of 10 ng/ml or less compared to a rate of 71% for patients beginning with a PSA greater than 10 ng/ml (table 3). The BRFS rate for low risk patients was 78% at 12 months compared to 72% for high risk patients (table 3). However, preoperative Gleason score did not affect freedom from biochemical recurrence at 12 month followup (74% for Gleason score 6 or less versus 76% for Gleason 7 or more). None of the above differences was statistically significant.

Finally, one must use caution when analyzing the 3-month data reported in table 3. Of these patients 37% received neoadjuvant hormone therapy for downsizing purposes or for high-grade cancers. However, all hormonal therapy was terminated at cryosurgery in all cases. One should still use caution when interpreting the 3-month data since PSA results may have been potentially biased by the lingering effects of neoadjuvant hormone therapy. Clearly, long-term followup of these patients is necessary to determine the ultimate role of cryosurgery in the treatment of prostate cancer.

Recent advances such as TRUS, urethral warmers and smaller diameter cryoneedles have significantly decreased complication rates associated with cryosurgery. In the current series there were no rectourethral fistulas or strictures reported, and scrotal swelling was 6% for all patients (salvage and primary cryotherapy). The incontinence rate for patients undergoing primary cryotherapy and requiring pads was 3%, while another 5% reported severe urge incontinence. In their meta-analysis Long et al performed a retrospective analysis of a large data base of patients (975) undergoing cryosurgery with older generation probes and compared their outcomes to contemporary reports of patients undergoing XRT.[14] In this review 975 patients undergoing cryosurgery reported a 7.5% incontinence rate compared to a range of 0% to 13% for patients receiving EBRT and 0% to 5% for patients receiving brachytherapy.[14] In this same review, rectourethral fistulas were reported in 0.5% of patients undergoing cryosurgery, 1% to 9% in patients treated with EBRT, and 0% to 7% in those treated with brachytherapy. The current series has no reports of fistulas thus far. Finally, with regard to erectile function 93% of patients undergoing cryosurgery were impotent after treatment compared to 37% to 70% for EBRT and 10% to 40% for brachytherapy.

As a greater number of patients select minimally invasive treatment options such as brachytherapy and EBRT in the hope of avoiding the morbidities associated with radical prostatectomy, urologists will see increasing numbers of treatment failures from such therapies. Salvage prostatectomies are associated with significant morbidities, and as a result, patients are often left with the option of either watchful waiting or temporary palliation with hormone deprivation therapy and its attendant toxicities. These patients may be potential candidates for salvage cryotherapy.

In the current series, 18 patients underwent salvage cryotherapy. The complication rates in these patients were either comparable to or less than those previously reported by other investigators. Table 4 compares the complication rates of recently published reports for patients undergoing salvage cryotherapy with a variety of cryosurgery technologies. The current series includes only 2 patients (11%) that reported the use of pads after salvage cryotherapy and no rectourethral fistulas. By comparison, initial salvage cryosurgery studies reported incontinence rates as high as 73%.[15] In addition, there were no fistulas reported in the current series. As a result, urologists should consider salvage cryosurgery as a minimally invasive alternative with its decrease in complication rates compared to previous salvage cryosurgery series.

Several issues were encountered in patients undergoing salvage cryosurgery. In patients who had previously undergone brachytherapy treatment, the seeds were echogenic on ultrasound, making placement of the cryoneedles slightly more challenging. The echogenic foci from the previously placed seeds could be confused with the echogenicity of the cryoneedles during insertion. In addition, even with the smaller 1.5 mm needles some degree of fibrosis was encountered during cryoneedle placement in most patients undergoing salvage cryosurgery. Urologists learning to perform cryosurgery should be aware of these considerations as well as the potential increased risk of incontinence in previously radiated patients.

This study is the result of a multi-institutional effort with data collected from urologists with different levels of experience. Some had significant experience with the older technologies, others with brachytherapy experience had a short learning curve, while others had no previous cryosurgery or brachytherapy experience. However, despite this wide spectrum of experience, the overall morbidities remained reasonable as reported here and are lower when compared to the older generation technologies.

Routine followup biopsies were not performed. While many prior studies[4,5,14,16] performed routine followup biopsies after cryosurgery, the urologists in the current study relied only on PSA levels for clinical outcome. Unless clinically warranted (ie PSA increase greater than 0.4 ng/ml), biopsies

TABLE 4. *Complications associated with salvage cryotherapy*

	Pisters et al[15]	Chin et al[17]	Ghafar et al[18]	Present Series (3rd generation)
% Incontinence	73	6.7	7.9	11 (pads)
% Obstruction	67	8.5	Not reported	0
% Impotence	72	Not reported	Not reported	89
% Fistula	1	3.3	0	0

in an otherwise clinically stable patient were deemed an unnecessary invasive procedure after an otherwise minimally invasive treatment for prostate cancer.

Finally, although these smaller 1.47 mm cryoneedles appear to be safer, the question remains with regard to long-term PSA control and ultimately survival: does placing more probes (12 to 15 needles in this series) versus 5 to 8 large probes (older series) provide more effective and accurate contouring of the ice balls? We are currently conducting animal studies to compare the efficacy of large 3.0 mm probes versus 1.5 mm needles in an effort to address this issue.

CONCLUSIONS

By permitting the use of 17 gauge (1.47 mm) cryoneedles, 3rd generation cryosurgery offers more precise prostatic ice ball formation and offers the flexibility to place an increased number of probes where necessary. With the evolution of TRUS guidance, urethral warmers and smaller needles, the morbidities associated with this treatment alternative have become comparable to other available treatment options and are within an acceptable range.

Long-term followup of PSA data and survival are necessary before any conclusions can be made regarding the efficacy of this minimally invasive option. Third generation cryosurgery should not only be considered in older or high risk medical patients who would not otherwise be considered for radical prostatectomy, but also in patients who present after failure of radiation therapy. In addition, as more patients select XRT, increasing the number of potential patients in whom treatment subsequently fails, salvage cryotherapy may potentially offer a more attractive alternative to salvage prostatectomy, hormone deprivation or watchful waiting.

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