Transrectal Ultrasound-Guided Percutaneous Radical Cryosurgical Ablation of the Prostate

Gary M. Onik, M.D., Jeffrey K. Cohen, M.D.,* George D. Reyes, M.D.,* Boris Rubinsky, Ph.D.,† ZhoaHua Chang, Ph.D.,‡ and John Baust, Ph.D.‡*

Background. The two major treatments for prostate cancer, radical prostatectomy and radiation therapy, are associated with considerable morbidity and variable results. This article presents the preliminary results using percutaneous radical cryosurgical ablation under ultrasound guidance to treat prostate cancer.

Methods. The patient group consisted of all patients with localized prostate cancer who underwent cryosurgery between June 1, 1990 and May 1, 1992. Patients in Group 1 were treated by freezing of the tumor with two cryoprobes placed multiple times. Group 2 patients were treated by freezing of the tumor with five cryoprobes placed simultaneously. Cryoprobes (3 mm in diameter) were placed percutaneously with a transperineal approach. Cryoprobe placement and freezing were monitored using the transrectal ultrasound.

Results. Of the 55 patients (68 procedures) undergoing treatment, 23 have 3 months of follow-up with associated biopsy (Group 1, 8 patients; Group 2, 15 patients). In Group 1, three (37.5%) patients had residual disease. In Group 2, one (6.7%) patient had residual disease, whereas 14 (93.3%) patients did not. Combining both groups, 19 (82.6%) patients had no residual disease, whereas 4 (17.4%) patients had positive results on postoperative biopsy. Complications included rectal freezing, urethrorectal fistula, sloughing urethral tissue, impotence, perineal ecchymosis, penile edema, and ileus.

Conclusions. Preliminary results indicate that percutaneous transperineal ultrasound-guided prostate cryosurgery may be an effective treatment for prostate cancer with minimal associated morbidity. _Cancer_ 1993; 72: 1291–9.

From the *Departments of Neurosurgery and Urology, Allegheny General Hospital, Pittsburgh, Pennsylvania; the †Department of Mechanical Engineering, University of California Berkeley, Berkeley, California; and ‡Cryomedical Sciences, Inc., Rockville, Maryland.

Address for reprints: Gary M. Onik, M.D., Department of Neurosurgery, Allegheny General Hospital, 320 East North Avenue, Pittsburgh, PA 15212.

Accepted for publication March 26, 1993.

Key words: adenocarcinoma, prostate, ultrasound, percutaneous, transperineal, prostate-specific antigen.

Prostate cancer is recognized as one of the most prevalent malignant diseases occurring in men. It is estimated that it will cause the deaths of 34,000 men in 1992. In addition, approximately 132,000 cases of prostate cancer will be diagnosed in 1993.[1] As the use of prostate-specific antigen and transrectal ultrasound increases, the number of newly diagnosed cases of prostate cancer will increase.

The two major treatment options for prostate cancer, radical prostatectomy and radiation therapy, are associated with considerable morbidity. Before radical prostatectomy, a pelvic lymphadenectomy is performed to assess whether or not spread has occurred. If the nodes are negative, radical prostatectomy is performed.[2] However, if they are positive, the radical prostatectomy is avoided, thus sparing the patient the major morbidity associated with the procedure, including incontinence, impotence, blood loss with consequent transfusion-related complications, and damage to adjacent structures. In addition, a disturbing trend has been reported in that the surgical margin of the prostate after radical prostatectomy contains disease 33–56% of the time.[3–5]

Radiation therapy is associated with many of the same problems as radical prostatectomy. There are substantial complications associated with radiation therapy, including thrombophlebitis, lymphocele formation, pulmonary embolism, wound infections, impotence, incontinence, and late complications, including radiation proctitis and cystitis.[6,7] In addition, recent studies using transrectal ultrasound-guided biopsies showed residual tumor in 80–93% of patients 2 years after radiation treatment.[8,9]

Prostate cryosurgery, the in situ freezing of prostate cancer, has been suggested and used in the past as an alternative in patients who could not undergo radical prostatectomy or radiation therapy.[10] The major advantages of cryosurgery were the minimal amount of bleeding and low surgical morbidity associated with it. In addition, the long-term survival data in previous studies showed that cryosurgery was equal to radical prostatectomy and radiation therapy.[11] However, prostate cryosurgery never gained widespread acceptance because of the complications of tissue sloughing and fistulization.

Technical advances have occurred since Bonney et al.[11] and Gondor et al.[12] first attempted prostatic cryosurgery. Transrectal ultrasound and percutaneous tissue accessing techniques (such as those used in endourologic procedures) are widely practiced by radiologists and urologists. These techniques have increased the possibility of decreasing the morbidity associated with earlier work. In a recently published study by Onik et al.,[13] the ultrasound characteristics of frozen prostatic tissue were characterized, indicating that the freezing process could be monitored under real-time ultrasound control. The edge of the freeze zone is visualized as a hyperechoic rim emanating from the cryoprobe with posterior acoustic shadowing. Additional animal studies have shown that percutaneous transperineal placement of cryoprobes with ultrasound monitoring could be performed with no associated morbidity.[14]

This article presents the preliminary results showing the feasibility of using percutaneous radical cryosurgical ablation under ultrasound guidance to treat prostate cancer. Radical cryosurgical ablation (RCSA) is defined as the freezing of the entire prostate gland, periprostatic tissue, neurovascular pedicles, and proximal seminal vesicles.

Patient Selection and Evaluation

The patient group consists of all patients who underwent prostate cryosurgery from June 1, 1990 through May 1, 1992. All patients had biopsy-proven disease and were staged according to the Jewett classification.[15] In the patients who were evaluated initially at Allegheny General Hospital, staging biopsies included possible sites of extracapsular extension. Many patients (>75%) had biopsies done elsewhere. In general, these did not include biopsies of tissue outside of the prostate. A bone scan, computed tomography scan, chest radiograph, complete blood cell count, prostate-specific antigen (PSA), and acid phosphatase levels were obtained on all patients. If the preoperative PSA was more than 10 ng/ml, a pelvic lymphadenectomy was performed by open or laparoscopic technique. Patients were excluded if they had any of the following: an uncontrollable bleeding or coagulation disorder, an active genital or urinary tract infection (including prostatitis), or the inability to grant informed consent.

Each patient was evaluated with a digital rectal examination, transrectal ultrasound, and an ultrasound-guided biopsy of the prostate gland before the procedure. Transrectal ultrasound was used to diagnose disease and perform biopsies in all patients, except those with Stage A disease. Patients underwent biopsy again 3 months after the procedure using the method outlined by Kabalin et al.[8] and modified by Lee et al.[9] These postoperative biopsies were done at the site of previous cancer and at random sites throughout the prostate gland and periprostatic tissue. Any patient receiving hormone-suppressive therapy before the procedure had this therapy discontinued after the procedure. Prostate specific antigen values were obtained before the procedure, in the recovery room postoperatively, on postoperative day one, at 6 weeks, 3 months, and at 3-month intervals thereafter. Additional biopsies were obtained if a rising PSA value was detected.

Approval for this program was granted after review by the Institutional Review Board of Allegheny General Hospital. Informed consent was obtained from all patients. All patients were made aware of the fact that Drs. Onik and Cohen have a financial interest in Cryomedical Sciences. In an effort to eliminate possible bias by the authors, the data were reviewed and confirmed by an independent observer.

Technique

The technique of prostate cryosurgery using transrectal ultrasound as a guide evolved as experience was gained through our initial patient treatments. The first two patients had half of the prostate frozen at one time. Both returned 2 months later to have the other half treated. Because these two patients appeared to have no complications, six more patients underwent treatment of the entire prostate in one procedure between August 1991 and March 1991. These eight patients make up Group 1. Because cryogenic systems available at the time had only one probe available per instrument, freezing of the entire prostate gland was performed using two instruments with one probe each placed into the gland multiple times.

Early biopsy and PSA results indicated that with this technique, total gland destruction was not occurring. To correct this problem, a new, high-capacity, freezing system was developed (Cryomedical Sciences, Inc., Rockville, MD) in which five probes could be used simultaneously. This new system was used in all of the patients treated from October 1991 through May 1992. These patients make up Group 2.

In our current procedure, a mechanical bowel preparation and neomycin base (1 g) and erythromycin (1 g)

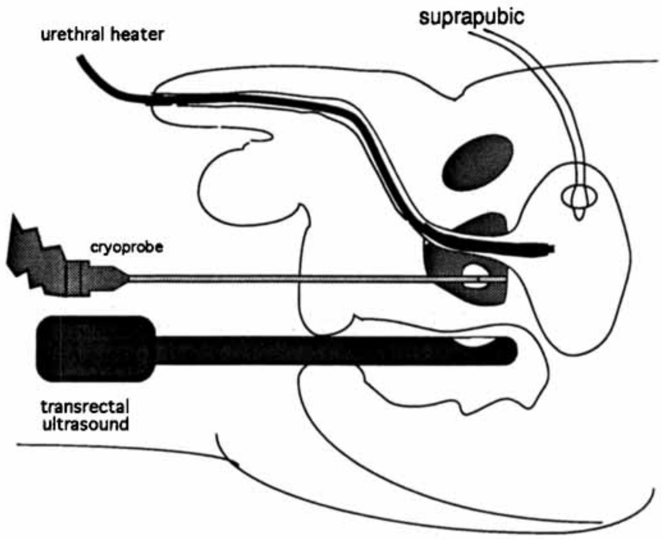

Figure 1. Diagram showing the relationship of the cryoprobes to the prostate and transrectal ultrasound.

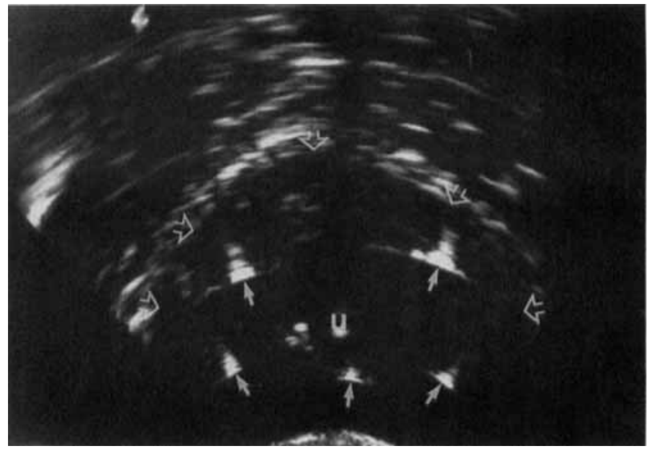

Figure 2. A prostate gland with five probes placed within it. The prostate gland (open arrows) in a transverse view under transrectal ultrasound is seen with five probes placed within it (solid arrows). To cover the full extent of the prostate, it is critical to have two anterior probes, two posterior probes, and one probe directly behind the urethra (u = urethra).

were administered at 1:00, 2:00, and 11:00 p.m. on the day before surgery. Intravenous gentamycin and cefazolin were given the morning of surgery before the procedure. Intravenous antibiotic administration was continued during the postoperative period for 24 hours. Oral antibiotic administration was continued until the suprapubic tube was removed. The perineum of the patient was prepared and draped in a sterile manner. Flexible cystoscopy was performed, and a percutaneous suprapubic tube (10 French Cope Loop Catheter, Cook Urological, Spencer, IN) was inserted under direct vision. The urethral warming device was inserted. This device is a modified angioplasty catheter that circulates water heated to 44°C. Using an Aloka 7.5 MHz longitudinal and a 5 MHz transverse transrectal ultrasound transducer (Aloka, Wallingford, CT), the prostate was surveyed and volume measurements were made.

Using the attached biopsy guide, a diamond tip, 18-gauge needle was placed into the preselected area of the prostate under ultrasound guidance. When appropriately placed within the prostate, as confirmed by ultrasound, a 0.038 J-tipped wire with nontapered mandril was passed through the needle to the most cephalad extent of the prostatic capsule. A cannula and dilator were placed over the wire into the prostate. The cannula was positioned against the most cephalad prostatic capsule, and the dilator and wire were removed. The cryoprobe was placed into the prostate through the cannula (Fig. 1). This was repeated with as many as five cryoprobes to cover the entire prostate gland. Cryoprobes were placed in approximately the same arrangement, regardless of tumor location. The cannulas were retracted. When all of the probes were confirmed with ultrasound to be correctly positioned within the prostate (Fig. 2), liquid nitrogen was circulated within the probes. The process was monitored with ultrasound so that the posterior rim of the freeze zone was used as a guide for discontinuation of freezing. When that rim had passed through the prostatic capsule, before reaching the rectal wall, the probes were deactivated (Fig. 3).

When necessary, the five probes were withdrawn to the apex of the prostate gland and a repeat freezing cycle performed to ensure that the freezing zones overlapped, thus covering the entire prostate. Care was taken during the procedure to stop the process before transmural rectal freezing. Once the cycle was completed, the probes and urethral warming device were

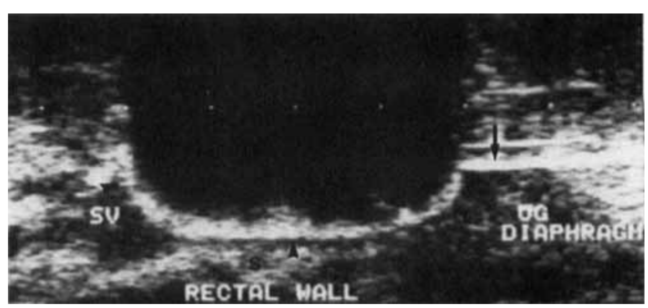

Figure 3. Sagittal view showing the appearance of the ice ball in its relationship to prostatic structures. The extent of the ice ball is noted as a hyperechoic rim emanating from the cryoprobe (arrowheads indicating hyperechoic rim, arrow indicating cryoprobe). The freezing extends into the inferior aspect of the seminal vesicle (sv) and enters the space (s) between the rectal wall and the prostatic capsule. In this freezing, the inferior extent of the freezing did not extend through the urogenital diaphragm, necessitating the pulling back of the probe.

Table 1. Results of Percutaneous Prostate Cryosurgery (Group 1)

Patient	Age	Stage	Grade	Radiation failure	Previous hormones	No. of cryosurgery procedures	Before PSA	After PSA	After biopsy
1	67	B2	6	No	No	3	10.2	0.6	−
2	69	B2	8	No	Yes	4	8.0	2.0	+
3	59	B1	6	No	Yes	1	6.4	2.0	−
4	51	C	WD	No	No	3	6.7	3.2	−
5	63	B1	7	No	No	2	1.93	0.0	−
6	67	B2	7	Yes	No	3	13.0	10.9	+
7	66	C	5	No	No	1	2.5	0.0	−
8	58	C	7	No	Yes	1	77.8	23.9	+

PSA: prostate-specific antigen; WD: well differentiated.

removed. The patients returned to the recovery room with the suprapubic tube for drainage. This usually was capped 24 hours later, with the patient being discharged from the hospital after 48 hours. The suprapubic tube was removed when the postvoid residual was less than 100 ml.

Results

Between June 1, 1990 and May 1, 1992, 68 procedures had been completed on 55 patients (47 patients with one procedure, 4 patients with two procedures, 3 patients with three procedures, and 1 patient with four procedures); 23 patients have more than 3 months of follow-up with associated biopsy study. Postoperative biopsies were done 3 months after each cryosurgical treatment. Post-PSA results were taken from 6 weeks to 18 months (mean, 6.75 months) after the last cryosurgery procedure. PSA results returned to normal by the 6-week follow-up date and remained stable in patients without residual cancer or distant metastases. Group 1 consisted of the eight patients who were treated with the older version of the cryoablation system. Five of these eight (62.5%) patients had multiple procedures. Group 2 consisted of 47 patients treated with the new cryoablation system. Only three of these 47 (6.4%) patients had two cryosurgical treatments. Because Group 1 patients were treated using the suboptimal freezing equipment and technique, the data were analyzed separately for these 8 patients and the 47 patients treated with the new system.

Follow-up on the eight patients of Group 1 ranged from 18 to 27 months from their first cryosurgical procedure (mean, 23.5 months) (Table 1). Of the eight patients treated in Group 1, three (37.5%) had residual disease after the procedure. Two of these three patients received treatment using the new equipment, and the third patient decided to undergo radiation therapy.

Preoperative evaluation of these eight patients revealed that one had external beam radiation therapy, three had hormonal deprivation, and none had prostate surgery before undergoing cryoablation. Two patients had Stage B1, three had Stage B2, and three had Stage C prostate cancer. Of the three patients with residual cancer, two had Stage B2 cancer, and one had Stage C cancer. Gleason grades were as follows: one with 5 of 10, two with 6 of 10, three with 7 of 10, one with 8 of 10, and one well-differentiated cancer with no Gleason grade specified. Gleason grades in the group with residual cancer were two 7 of 10 and one 8 of 10.

The mean (plus or minus the standard deviation [±SD]) preoperative PSA values for the patients with residual cancer (n = 3) and those without residual cancer (n = 5) were 32.9 ± 38.9 ng/ml and 5.5 ± 3.4 ng/ml, respectively. The mean (±SD) postoperative PSA values for these two groups was 12.3 ± 11.0 ng/ml and 1.2 ± 1.4 ng/ml, respectively.

Of the 47 patients whose prostates were frozen with the new cryoablation technology (Group 2), 15 have long enough follow-up and are evaluable with postoperative biopsy results (Table 2). Of these 15 patients two had prior radiation treatments, three had hormonal deprivation, and one had a transurethral resection of the prostate before undergoing cryoablation. Three patients had Stage A1, five had Stage B1, four had Stage B2, and three had Stage C prostate cancer. Gleason grades were as follows: four with 3 of 10, two with 4 of 10, three with 5 of 10, one with 6 of 10, one with 7 of 10, one with moderately differentiated cancer with no Gleason grade, and three with well-differentiated cancer with no Gleason grade. Results in relation to stage and grade of tumor are shown in Tables 3 and 4.

Follow-up on these patients at 3 months after the procedure shows that of these 15 patients, 1 (6.7%) has positive postoperative biopsy results (residual cancer), whereas 14 (93.3%) have negative biopsy results (no residual cancer). Negative biopsy results showed a uniform stromal reaction with no evidence for prostatic

Table 2. Results of Percutaneous Prostate Cryosurgery (Group 2)

Patient	Age	Stage	Grade	Radiation failure	Previous hormones	No. of cryosurgery procedures	Before PSA	After PSA	After biopsy
9	68	A1	4	No	No	1	3.73	1.1	−
10	70	B1	3	No	No	1	3.3	1.6	−
11	67	A1	3	No	No	1	10.1	3.4	−
12	57	C	WD	No	Yes	2	0.70	0.9	+
13	58	C	5	No	No	2	42.97	9.8	−
14	61	B1	3	No	No	1	3.5	0.6	−
15	70	B2	6	No	No	1	3.6	0.4	−
16	60	B1	7	No	Yes	1	8.6	0.15	−
17	71	B2	5	No	No	1	19.6	0.4	−
18	70	B2	MD	Yes	No	1	6.7	0.71	−
19	73	C	WD	Yes	Yes	1	0.08	0.0	−
20	51	B1	3	No	No	1	6.39	0.0	−
21	73	B2	5	No	No	1	10.11	1.4	−
22	58	A1	WD	No	No	1	9.2	1.3	−
23	67	B1	4	No	No	2	5.8	0.0	−

PSA: prostate-specific antigen; WD: well-differentiated; MD: moderately differentiated.

epithelial elements (Fig. 4). This residual cancer group included one patient with well-differentiated, Stage C cancer who has received subsequent treatment with subsequent biopsy results pending.

Of the 15 patients with follow-up biopsies, the mean preoperative PSA value for the patients without residual cancer (n = 14) was 9.5 ± 10.7 ng/ml, whereas the mean postoperative PSA value for these patients was 1.5 ± 2.6 ng/ml. However, one patient (Patient 13) with a negative biopsy has a high PSA value (9.8), which may be attributable to cancer outside of the prostate. Without this patient to skew the results, the preoperative and postoperative PSA values for patients without residual cancer are 7.0 ± 4.9 ng/ml and 0.9 ± 0.9 ng/ml, respectively.

When Groups 1 and 2 are combined, there are 23 patients with follow-up times of 3 months or more. Of these, 4 (17.4%) patients have residual cancer, whereas 19 (82.6%) patients have no residual cancer.

Complications in the entire group of 55 patients (68 procedures) included freezing of the rectum in 4 patients (5.9%), which resulted in urethrorectal fistula in 2 patients (2.9%) and sloughing of prostatic urethral tissue in 3 patients (4.4%). Of the 23 patients with follow-up times of 3 months or longer, 20 had prepotency and postpotency data. Fourteen of the 20 were potent before cryosurgery, whereas 6 of the 20 were impotent. After the procedure, five (35%) patients retained their potency, and nine did not. However, follow-up for most of these patients was 6 months or less. Other complications included perineal ecchymosis, penile edema, and ileus, all of which resolved. There has been no mortality associated with this procedure.

Discussion

In 229 patients with prostate cancer reported by Bonney et al.,[16] the advantages of cryosurgery included minimal blood loss, the ability to treat patients with high-stage disease, and a decrease in the impotence rate compared with that associated with radical prostatectomy. In addition, the survival rate in patients treated with cryotherapy in every stage of the disease compared favorably to radical prostatectomy or external-beam radiation therapy. However, complications from

Table 3. Biopsy Results According to Stage

Stage	No. of patients	Positive biopsy findings No.	%
A1	3	0	0
B1	7	0	0
B2	7	2	29
C	6	2	33

Table 4. Biopsy Results According to Gleason Grade

Grade	No. of patients	Positive biopsy findings No.	%
2–4 Well-differentiated	10	1	10
5–7 Moderately differentiated	12	2	17
8–10 Poorly differentiated	1	1	100

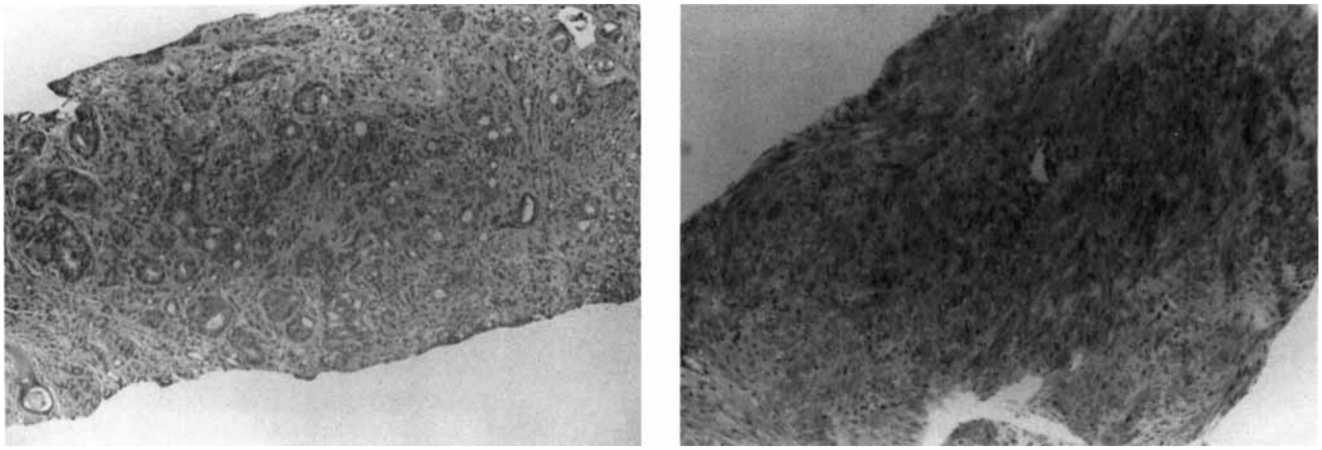

Figure 4. (Left) Preoperative biopsy showing a moderately differentiated adenocarcinoma of the prostate. (Right) Postoperative biopsy showing no glandular elements, with the prostate tissue appearing as fibrous stroma. The distal and proximal cores (not shown here) also showed no residual tumor.

cryosurgery in this study included urethrorectal fistula in 1.4% of patients and urethrocutaneous fistula in 10.7% of patients. These complications were attributed to inadequate monitoring and control of the freezing process and the need for an open perineal approach.

Numerous factors have allowed for re-examination of prostate cryosurgery. Transrectal ultrasound shows the extent of the gland, accurately depicts probe placement, and allows for the real-time monitoring of the freezing process. In an initial pilot study that was undertaken in dogs to evaluate the feasibility of ultrasound monitoring of prostate cryosurgery, the process was easily visualized as a hyperechoic rim emanating from the cryoprobe.[14] In this study, coagulative necrosis was seen in the dogs that were killed immediately after the procedure and those killed 2 weeks later. In addition, the glandular acini were destroyed by the cryosurgical procedure. Although absorption of cryosurgically treated tissue takes place sometime within the first 3 months, it is unknown exactly when the tissue is totally absorbed.

Prior experience with prostatic cryosurgery demonstrated the need for a perineal incision to access the gland. This resulted in the urethrocutaneous fistulas. Percutaneous access techniques as developed for endourologic procedures are reapplied to this process, thus eliminating the need for a perineal incision. We also are able to use multiple small-diameter (3 mm) probes as opposed to one larger (8 mm) probe placed several times. The activation of multiple probes allows for a larger frozen zone, one that exceeds the dimensions of the prostate. In addition, the technical advances in the freezing equipment allow for a larger volume of frozen tissue compared with the equipment available circa 1960. However, patients with prostate gland volumes greater than 50 g either had their glands down sized with hormone suppressive therapy or required two cryosurgical treatments.

Our results, although preliminary, indicate that a relatively noninvasive RCSA procedure such as that we have described can successfully destroy prostate cancer, resulting in an overall rate of negative findings on biopsy of 82.6%, with a residual rate of positive findings on biopsy of 17.4% at 3 months. The positive biopsy rate for patients with larger tumors (Stages B2 or C) is higher (31%) than that of the total population. As we have gained greater experience, we have made improvements in probe placement, including placing more probes (as many as seven) and placing probes into the periprostatic tissue. We routinely treat the periprostatic tissue, regardless of the initial staging. The extension of the ice ball into the periprostatic tissue is entirely safe. The ice ball can be extended in the lateral direction by any degree, in the posterior direction until it reaches the rectum, and in the superior direction by any degree (thus far, no complications have been seen by freezing the bladder). We hope that this will decrease the number of patients with Stage B2 or Stage C residual cancer. In addition, patients with residual cancer can undergo cryosurgery again if they desire. Although long-term follow-up with repeat biopsies at 1 and 2 years and survival data must be accumulated, our initial results compare favorably with the transrectal ultrasound-guided biopsy results obtained after radiation therapy.[8]

Ultimately, RCSA may prove to be superior to radical prostatectomy because of the technical advantages of being able to freeze and treat difficult areas, such as the apex of the gland, and the periprostatic tissue, including the neurovascular pedicles and seminal vesicles, which account for the positive surgical margins

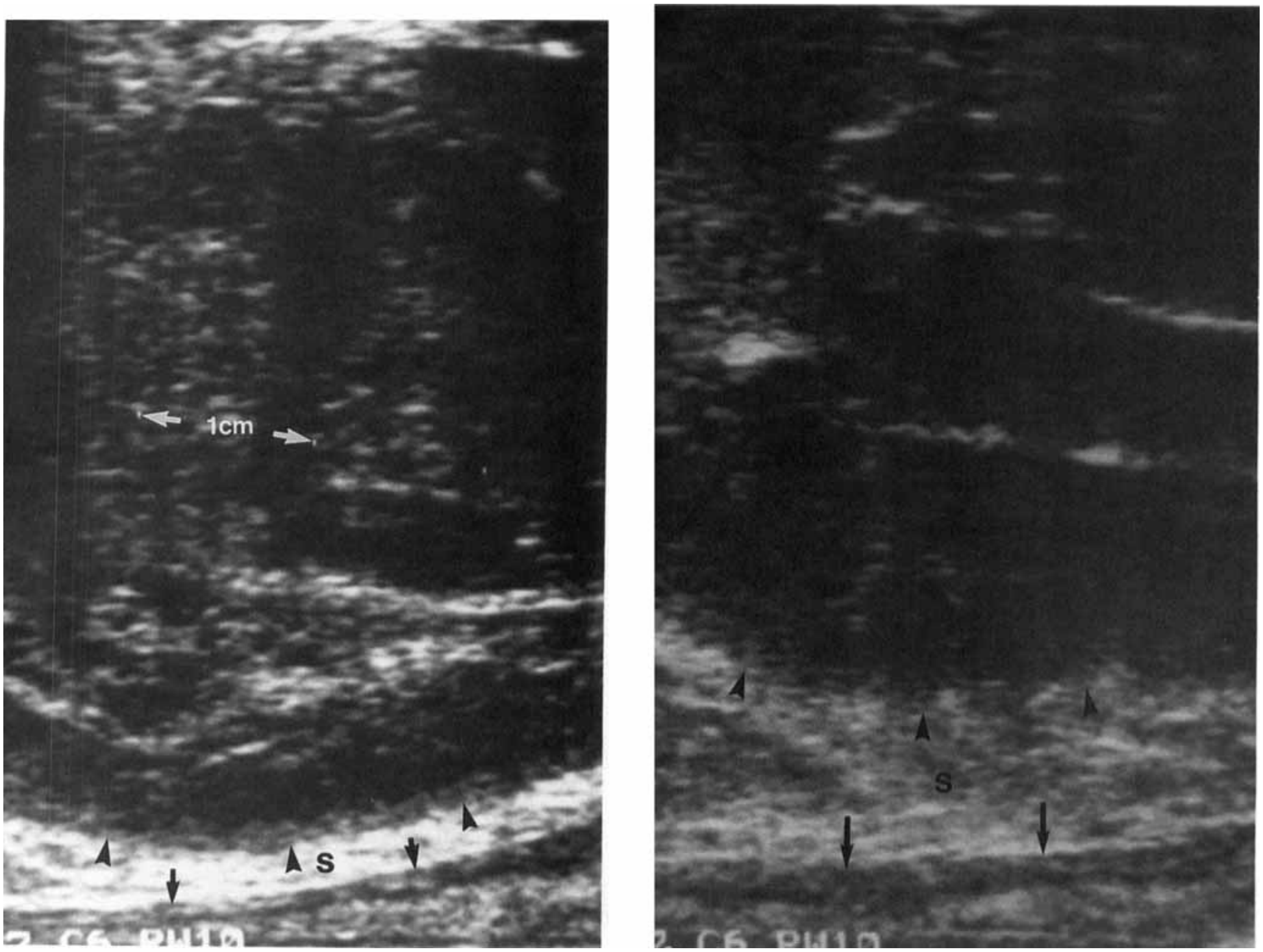

Figure 5. (Left) Illustration showing the increase in space (s) behind the prostatic capsule between the rectum and the prostate with manipulation of the ultrasound probe. The relationship of the prostatic capsule (arrowhead) to the rectum (arrow) is noted. (Right) With manipulation of the transrectal probe, the space (s) can be increased from 44 mm to larger than 1 cm (distance scale the same as that seen in 4, left). This allows freezing beyond the prostatic capsule into space behind the prostate without injury to the rectal wall.

and the ability to again treat patients who initially have positive biopsy results. Transrectal ultrasound-guided biopsies can evaluate areas of extracapsular disease, most notably the neurovascular bundles, seminal vesicles, and ejaculatory ducts. Once extracapsular disease has been found, it can be treated by allowing the freezing process to continue through the prostatic capsule into the periprostatic tissue and by placing probes outside of the capsule to freeze these areas. Thus far, we have seen a postoperative negative biopsy rate of 67% in patients with Stage C disease.

It initially was thought that RCSA might be limited because of the proximity of the prostate to the rectum and external sphincter. However, it was found through experience that an increased space between the rectum and the prostatic capsule could be created in most patients (Fig. 5). This was accomplished by raising the handle of the transrectal ultrasound probe. This pushes the tip of the probe against the posterior wall of the rectum, pulling the rectum off of the prostate. We routinely freeze through the urogenital diaphragm to treat apical tissue and the trapezoidal space in the method described by Lee et al.[17]

None of our patients has incontinence, thus demonstrating the safety of freezing through the urogenital diaphragm. This preservation of continence may in part be attributable to preservation of the internal sphincter; however, even patients who have undergone previous transurethral resection of the prostate remain continent.

Early detection of carcinoma has been facilitated by PSA. The absolute value and postoperative trend of PSA have led to the earlier discovery of residual disease. Not all of our patients with negative biopsy results (fibrotic tissue only) have postoperative PSA values of zero. This situation could reflect one of the following: (1) residual normal tissue (at the apex or around the urethra); (2) residual cancer missed by the biopsy (patients will be followed up with PSA tests and another biopsy if the PSA continues to rise); or (3) adequate local treatment in patients with subclinical nodal or distant disease. All but one of our patients with positive results on biopsy had normal results on rectal examination postoperatively, but ultrasound-guided biopsies were able to confirm the presence of residual disease.

Patients who have positive biopsy results after cryosurgery can undergo repeat treatment, radiation therapy, or radical prostatectomy. The difficulty of performing radical prostatectomy after cryosurgery is unknown because none of our patients has chosen that option. The ability to administer radiation therapy after cryotherapy has been demonstrated in the literature and remains an option for patients.[18] A major advantage of cryosurgery is the ability to subsequently treat a patient with minimal morbidity. Our data show that eight patients had subsequent treatment, with five of them (thus far) reverting from positive to negative results on biopsy.

As we have demonstrated, patients for whom radiation therapy failed can undergo cryosurgical ablation with minimal morbidity. Three of the patients treated with cryosurgery had previously undergone radiation therapy. Two of these patients have achieved negative biopsy results with no morbidity.

As with any procedure, there is an initial learning curve. As we gained experience, the procedure changed in several ways. However, the most significant change occurred with the introduction of a multiple cryoprobe system that could adequately freeze the entire gland at once. This accounted for the separation of the first 8 patients (Group 1) from the last 15 (Group 2), in whom the difference of positive biopsy results was 37.4% and 6.7%, respectively. It is clear that ultrasound cannot reliably reveal the full extent of disease, thereby making it impossible to successfully pinpoint the tumor and selectively destroy it. Complete prostate destruction is the goal of therapy, especially because prostate cancer often is multifocal. Our early experience indicated that this goal is not possible with one or even two probes placed sequentially. Only when a five-probe system was developed and used could the entire prostate and the immediately adjacent tissue be treated simultaneously.

Although this procedure appears to be associated with low morbidity, complications occurred. This was, in part, attributable to inexperience with the procedure. It was thought that ultrasound monitoring could prevent the previously reported problem of urethrorectal fistula; however, despite ultrasound monitoring, rectal freezing occurred in four patients. Two of these patients subsequently had urethrorectal fistulas (Procedures 15 and 17), which were not attributable to an inadequacy of ultrasound monitoring. They were caused by the volume of frozen tissue continuing to expand (approximately 4 mm) despite the flow of liquid nitrogen to the cryoprobe being stopped. This complication has not recurred since our appreciation of the situation.

The rate of impotence remains uncertain. One-third of patients who were potent before the procedure remained so. Prior reports of impotence range between 7% and 50%.[16,19] Because of the phenomenon of nerve regeneration, the final rate of impotency remains unknown.[20,21] At least one of our patients regained potency as late as 6 months after the procedure.

Our initial hesitancy to adequately freeze the apex of the prostate resulted in positive biopsy results in two patients. These patients have undergone subsequent treatment, and their biopsy results are negative.

In summary, we have described a new procedure that uses low temperatures to treat carcinoma of the prostate. The procedure is technically possible to perform with minimal morbidity because of the use of transrectal ultrasound, percutaneous access techniques, and a multiple cryoprobe delivery system. Our early data are encouraging. Previously incurred complications have been reduced, and follow-up is ongoing.

References

1. Cancer statistics. *CA* 1992; 42:21–38.
2. Schroder FH. What is the optimal treatment for early prostatic cancer? *Acta Oncol* 1991; 30:247–9.
3. Catalona WJ, Dresner SM. Nerve-sparing radical prostatectomy: extraprostatic tumor extension and preservation of erectile function. *J Urol* 1985; 134:1149–51.
4. Catalona WJ. Patient selection for, results of, and impact on tumor resection of potency-sparing radical prostatectomy. *Urol Clin North Am* 1990; 17:819–26.
5. Jones EC. Resection margin status in radical retropubic prostatectomy specimens: relationship to type of operation, tumor size, tumor grade and local tumor extension. *J Urol* 1990; 144:89–93.
6. Porter AT. Is radiotherapy of use in Stage C prostate cancer? Therapeutic progress in urological cancers. *Prog Clin Biol Res* 1989; 303:211–8.
7. Sagerman RH, Chun HC, King GA, Chung CT, Dalal PS. External beam radiotherapy for carcinoma of the prostate. *Cancer* 1989; 63:2468–74.
8. Kabalin JN, Hodge KK, McNeal JE, Freiha FS, Stamey TA. Identification of residual cancer in the prostate following radiation therapy: role of transrectal ultrasound guided biopsy and prostate specific antigen. *J Urol* 1989; 142:326–31.
9. Lee F, Torp-Pedersen S, Meiselman L, Siders DB, Littrup P, Dorr RP, et al. Transrectal ultrasound in the diagnosis and staging of local disease after I^{125} seed implantation for prostate cancer. *Int J Radiat Oncol Biol Phys* 1988; 15:1453–9.

10. Addonizio JC. Another look at cryoprostatectomy. *Cryobiology* 1982; 19:223–7.
11. Bonney WW, Henstorf JE, Emaus SP, Lubaroff DM, Feldbush TL. Immunostimulation by cryosurgery: an orthotopic model of prostate and bladder cancer in the rat. *Natl Cancer Inst Monogr* 1978; 49:375–81.
12. Gondor MJ, Soanes WA, Shulman S. Cryosurgical treatment of the prostate. *Invest Urol* 1966; 3:372.
13. Onik G, Cobb C, Cohen J, Zabkar J, Porterfield B. US characteristics of frozen prostate. *Radiology* 1988; 168:629–31.
14. Onik G, Porterfield B, Rubinsky B, Cohen J. Percutaneous transperineal prostate cryosurgery using transrectal ultrasound guidance: animal model. *Urology* 1991; 37:277–81.
15. Jewett HJ. The present status of radical prostatectomy for Stage A and Stage B prostatic cancer. *Urol Clin North Am* 1975; 2:105–24.
16. Bonney WW, Fallon B, Gerber WL, Hawtrey CE, Loening SA, Narayana AS, et al. Cryosurgery in prostatic cancer survival. *Urology* 1982; 14:37–42.
17. Lee F, Torp-Pedersen ST, Siders DB. The role of transrectal ultrasound in the early detection of prostate cancer. *CA* 1989; 39:337–60.
18. Mobley WC, Loening SA, Narayana AS. Combination perineal cryosurgery and external radiation therapy for adenocarcinoma of prostate. *Urology* 1984; 24:11–4.
19. Kunit G. 'Open perineal cryosurgery' in carcinoma of the prostate-a possible curative alternative. *Urol Res* 1986; 14:3–7.
20. Kuflik EG, Gage AA. Cryosurgical treatment of skin cancer. New York: Igaku-Shoin, 1990.
21. Trumble TE, Whalen JT. The effects of cryosurgery and cryoprotectants on peripheral nerve function. *J Reconstr Microsurg* 1992; 8:53–8.