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FOCAL "NERVE-SPARING" CRYOSURGERY FOR TREATMENT OF PRIMARY PROSTATE CANCER: A NEW APPROACH TO PRESERVING POTENCY

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ABSTRACT

Objectives. To present a pilot study in which 9 patients treated with focal, unilateral nerve-sparing cryosurgery were followed for up to 6 years. Cryosurgery, in which the whole gland is frozen, has a high rate of impotence, similar to non-nerve-sparing radical prostatectomy.

Methods. Before focal nerve-sparing cryosurgery, all patients underwent repeated biopsy on the side opposite the previous positive biopsy. One neurovascular bundle was spared on the side opposite the positive biopsy. Just before the start of freezing, a 22-gauge spinal needle was placed into Denonvilliers fascia using a transperineal route, and saline was injected to separate the rectum from the prostate. Combined hormone therapy was stopped in all patients postoperatively. The prostate-specific antigen (PSA) level was obtained every 3 months for the first 2 years and then every 6 months thereafter. Patients were considered to have a stable PSA if they had two consecutive PSA measurements without a rise. All patients were strongly encouraged to undergo routine biopsies despite a stable PSA level.

Results. Between June 1995 and November 2000, 9 patients underwent focal, nerve-sparing cryosurgery. The follow-up ranged from 6 to 72 months (mean 36). All patients had stable PSA levels at last follow-up. Six patients routinely biopsied had negative biopsies. Potency (defined as an erection sufficient to complete intercourse to the satisfaction of the patient) was maintained in 7 of 9 patients.

Conclusions. Focal nerve-sparing cryosurgery, in which one neurovascular bundle is spared, appears to preserve potency in most patients without compromising cancer control. These preliminary results warrant further study.

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Radical prostatectomy (RP) is the reference standard in localized prostate cancer treatments. It was the seminal work of Walsh and Donker[1] that demonstrated that, by sparing the neurovascular bundles (NVBs), potency rates could be raised from the 1% to 2% associated with traditional RP to approximately 70% in their series. This obviously made RP a more palatable option for young patients especially and resulted in a marked increase in the application of nerve-sparing RP in the past decade.

Nerve-sparing RP still has significant associated limitations, however. The reported potency rates of nerve-sparing RP have varied widely in published studies from 18%[2] to 63%[3] in non-Johns Hopkins-related series. In addition, nerve-sparing RP is associated with general operative morbidity (ie, blood loss, infection) but also procedure-specific morbidity such as significant incontinence rates as high as 6%.[3] Also, the positive margin rate for nerve-sparing RP has been reported as high as 40% in series from major academic medical centers.[4,5]

Open transperineal prostate cryosurgery was first introduced in the early 1970s as a treatment for prostate cancer but, despite good long-term results reported,[6] never gained popularity. With the addition of a percutaneous approach and ultrasound monitoring, as reported by Onik *et al.*[7] in

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1993, prostate cryosurgery was re-examined as a treatment for primary prostate cancer. In an effort to validate percutaneous prostate cryosurgery as an effective treatment, protocols have been aimed at total gland ablation. Aggressive cryosurgery, including the periprostatic tissue with both NVBs, has a significant impact on sexual functioning. Virtually 100% of patients can expect to be impotent in the short term, with some patients recovering potency over a long period. Cryosurgery's strengths are the ability to tailor the procedure to the extent of the patient's disease and the unique ability of cryosurgery to be repeated with no added morbidity.[8] We believed on the basis of these strengths that an attempt to improve sexual functioning after cryosurgery was feasible.

In this report, we present a pilot study in which cryosurgery was applied focally, as determined by the patient's disease extent, in an effort to perform "nerve-sparing" cryosurgery, with the aim of preserving patient potency and limiting other operative morbidity.

MATERIAL AND METHODS

Patient Selection

Patients were considered for focal nerve-sparing cryosurgery if, based on sextant biopsy findings, their cancer was confined to one prostate lobe and they were potent on the basis of patient history and the maintenance of potency was a primary concern of the patient. The usual cryosurgical informed consent was given. All patients were informed of the additional risk of tumor being left untreated in any tissue not frozen. Patients biopsied at other institutions underwent repeat biopsy on the side opposite the previously demonstrated tumor. The repeat biopsy protocol included five cores taken from the lateral peripheral zone and two to three cores taken from the medial peripheral zone. Patients receiving combined hormonal therapy before cryosurgery had the therapy stopped immediately after treatment.

Procedure

The ultrasound-guided percutaneous prostate cryosurgery procedure was the same as that originally described by Onik *et al.*[7] A urethral warmer was used in all cases. The following changes were made to the procedure to accommodate the concept of nerve sparing and to increase the safety and efficacy of the procedure:

1. The extent of freezing was tailored to the particular patient and was determined by the patient's clinical parameters, including tumor location, Gleason grade, stage, and prostate-specific antigen (PSA) level.
2. The NVB was destroyed on the side of the patient's tumor in all patients. An attempt was made to spare one NVB on the side opposite the tumor.
3. Cryoprobes were placed approximately 1 cm apart in the regions to be destroyed and within 5 mm of the capsule on the side of the tumor. A cryoprobe was placed into the confluence of the seminal vesicles, directly posterior to the urethra, to prevent seminal vesicle recurrence.
4. Temperature monitoring was carried out in critical locations such as the apex of the gland and the NVB on the side of the tumor to ensure adequate tumor destructive freezing temperatures of −35°C. Temperatures were monitored in the NVB opposite the tumor to prevent bundle destruction.
5. Before freezing, a 22-gauge spinal needle was placed into Denonvilliers fascia using a transperineal approach. Normal saline was then injected into the space to separate the rectum from the prostate.
6. An argon gas-based system was used to carry out the freezing (Endocare, Irvine, Calif), replacing the original liquid nitrogen freezing equipment.

Patient Follow-up

All patients were removed from combined hormonal therapy immediately after the procedure. The PSA level was obtained every 3 months for the first 2 years and every 6 months thereafter. Patients were considered to have a stable PSA level if they had two consecutive PSA determinations without a rise. All patients were advised to undergo routine biopsies, including both the treated and untreated side, regardless of their PSA stability. Follow-up biopsies followed the preoperative biopsy protocol already described and were reviewed by the pathologist on duty at the time. Patients were followed up by written questionnaire and telephone call. Patients were considered potent if they had erections sufficient for vaginal penetration and were satisfied with their sexual functioning.

RESULTS

Between June 1995 and November 2000, 11 patients underwent focal, nerve-sparing cryosurgery. The total number of patients to have cryosurgery during that period was 176. The focal cryosurgery patients therefore represented 6% of our total patient population during that period. The follow-up ranged from 6 to 72 months (mean 36). Two patients were lost to follow-up, leaving 9 patients for evaluation (Table I). Three of the patients underwent bilateral gland freezing with an attempt to only spare the NVB. One patient had only the area of the tumor with an appropriate margin around the tumor frozen. The remainder of the patients had one half of the gland frozen. All patients were potent preoperatively, although 1 patient was primarily treated with this technique to decrease the chance of postoperative incontinence. All the patients had stable PSA levels at last follow-up, with the postoperative PSA level stabilizing at some fraction of the preoperative level, depending on the extent of the gland freeze. Six patients, who were routinely biopsied, had negative biopsies. The mean and median preoperative PSA level was 8.02 and 7.01 ± 4.4 ng/mL, respectively. The mean and median postoperative PSA level was 1.47 and 0.72 ± 1.57 ng/mL, respectively. Biopsies of the treated areas in all patients showed coagulative necrosis, benign stroma, and inflammatory infiltrates. Biopsies in untreated areas showed benign normal prostate in all patients except one (sixth row in Table I), in whom one core showed low-grade prostatic intraepithelial neoplasia. No patient required additional treatment, including hormonal therapy, after the procedure for presumed

cancer recurrence. Potency was maintained in 7 of 9 patients.

One patient, who was impotent after the procedure (the first patient treated), had the NVB on the nerve-sparing side frozen to −20°C, probably accounting for the postoperative impotence. The second impotent patient was 72 years old with multiple medical problems and a history of a previous transurethral resection of the prostate (TURP), who was taking chronic steroids for asthma. Focal cryosurgery was originally carried out in this patient to minimize the chance of incontinence rather than for potency sparing. This patient required a postoperative TURP to remove sloughed tissue and had transient stress incontinence. No instances of other complications previously described with cryosurgery such as obstruction, incontinence, penile numbness, or fistula formation occurred.

COMMENT

The procedure we describe of focal "nerve-sparing" prostate cryosurgery was an attempt to combine the advantages of cryosurgery, that of excellent treatment of extracapsular extension[9] and low general morbidity, while preserving the patient's potency. The procedure we performed is a unique combination of an aggressive treatment on the side of the cancer, yet a "minimal" procedure on the side opposite the cancer. Despite the potential negative impact on the potency results, the NVB on the side of the tumor was aggressively destroyed in all patients. In an effort to destroy extracapsular tumor extension, freezing was extended more than 4 mm beyond the capsule. In addition, all patients except one, received freezing of the confluence of the seminal vesicles to eliminate the chance for seminal vesicle recurrence. This aggressive freezing on the side of the tumor was facilitated by a saline injection into Denonvilliers fascia to separate the rectum from the prostate.

Within the context of our mean follow-up of 36 months, this approach was successful in local cancer control, with no evidence of local recurrence in any of the patients at last follow-up. This has greater significance, because the patient population was not selected to ensure success in this regard. Five of 9 patients had T2 disease, 3 patients had Gleason grade 7 or greater, and 4 patients had PSA levels of 10 ng/mL or greater. In total, 7 of the 9 patients had one or more adverse prognostic criteria.

One of the difficulties with our treatment approach is defining a successful result in terms of cancer recurrence. In this procedure, variable amounts of prostatic tissue on the side opposite the tumor are knowingly left untreated. Depending on the degree of tissue untreated, we expect to see a postoperative PSA reading greater than 0.2 ng/mL; therefore, previous PSA criteria, which establish a successful result for procedures aimed at total gland ablation, could not be applied in this study. As in patients without prostate cancer, however, we would expect PSA stability (ie, no rise in PSA over time) in patients adequately treated. Currently, we define PSA stability as no rise in the PSA level on two consecutive determinations. This criterion is consistent with common sense clinical practice and has resulted in none of the patients treated to date needing additional workup or treatment for cancer recurrence. The validity of our definition of PSA success is also supported by the biopsy results, with all 6 patients biopsied negative in both the areas frozen and left untreated. It was our intention to re-biopsy every patient regardless of PSA stability; however, to our frustration, 1 patient, despite our urging, steadfastly refused repeat biopsy. The two most recent patients have not yet been biopsied, one a Jehovah's Witness with a stable PSA of 0.1 ng/mL had the biopsy deferred because of safety concerns. The last patient had not reached the 1-year biopsy date.

Our greatest concern with our approach was leaving a significant cancer untreated on the side opposite the aggressive cryosurgery. It is well known that prostate cancer is often multifocal, the recognition of which would probably constitute the major theoretical objection to our treatment protocol. Villers *et al.*,[10] however, showed that 80% of multifocal tumors, other than the dominant tumor preoperatively identified, are less than 0.5 cm^3, indicating that a significant percentage of multifocal tumors may not be of clinical significance. Djavan *et al.*[11] showed that patients with unifocal disease constituted 33% of their cases studied and could be reliably differentiated from patients with multifocal disease with a sensitivity of 90%. Patients with multifocal disease had a PSA density of the transition zone of greater than 1.5 $ng/mL/cm^3$ and a free/total PSA ratio of less than 9%.

It is well known that traditional imaging modalities of ultrasonography and magnetic resonance imaging are inadequate in determining the extent of disease in prostate cancer. This leaves systematic biopsy as the major tool for determining the extent of disease preoperatively. The usual sextant biopsy, which is the current standard of care, has demonstrated limitations, including a false-negative rate approaching 25%.[12] It has been demonstrated, however, that the optimization of biopsy results by a second set of biopsies and improved gland sampling can greatly diminish the chances of missing a significant multifocal tumor.[13] In addition, demonstration of negative biopsies on the

TABLE I. *Patient characteristics*

Age (yr)	Follow-up (mo)	Gleason Score	Preoperative PSA* (ng/mL)	Positive Cores (n)	Stage	Preoperative TURP
62	72	5	10.5	1	T1c	No
64	62	8	12.9	1	T2a	Yes
58	61	5	4	1	T2a	No
67	41	6	4.5	1	T1c	No
72	29	6	10.8	1	T1c	Yes
56	24	6	5.5	1	T2a	No
67	21	7	1.5	1	T2a	No
55	12	7	16.5	3 of 4 cores, right	T2b	No
64	6	3	6	1	T1c	No

KEY: PSA = prostate-specific antigen; TURP = transurethral resection of the prostate.
** Mean preoperative PSA 8.022222222 ng/mL (median 7.011111111, SD = 4.382065275).*
† Mean postoperative PSA 1.47222222 ng/mL (median 0.725, SD 1.57648782).

nerve-sparing side is an excellent predictor of negative margins at nerve-sparing RP.[14]

In an effort to exclude significant cancer, all our patients, but one, underwent a second set of biopsies focused on the side opposite the originally demonstrated tumor. All also received an optimized biopsy protocol, with five biopsies through the lateral peripheral zone and two to three biopsies through the medial aspect of the gland.

It should be noted that two of the patients we treated were younger than 60 years, a group in whom inadequate treatment could theoretically have an impact on patient survival. This factor certainly must be taken into account when considering a wider application of this treatment approach, as it must be with other potency-sparing procedures. A level of comfort in this regard is possible with focal cryosurgery, because, unlike nerve-sparing RP and brachytherapy, cryosurgery has the unique ability to allow repeated cryosurgical treatments without added morbidity.[8]

In actuality, one of the strengths of the procedure that we describe is the ability to tailor the procedure according to the threat of disease in the opposite prostate lobe. Three of our patients at high risk of multifocal disease underwent bilateral prostate freezing, with NVB sparing only on the side opposite the cancer; 2 of the 3 patients had good potency-sparing results, despite more extensive freezing. On the other hand, our most recently treated patient had a well-defined (on both magnetic resonance imaging and ultrasonography) 6-mm tumor of Gleason grade 3 and was at low risk of multifocal disease using the criteria of Djavan *et al.*[11] Biopsies surrounding the visible abnormality showed no cancer; therefore, a minimal, focal procedure, directed only to the visible tumor and a surrounding margin of tissue and NVB, was carried out. The reward for this minimal treatment was that the patient did not need a Foley catheter postoperatively and was sexually active 1 week after the procedure.

The procedure appears to have extremely low morbidity. No significant blood loss or perioperative cardiac or pulmonary complications occurred, nor were they expected, since even with total gland ablation these are not a problem. None of our patients had significant long-term incontinence after the procedure. One patient, who had undergone previous TURP and was taking chronic steroids for asthma, underwent focal cryosurgery in an attempt to decrease the incidence of urinary complications. He had mild stress incontinence after TURP to remove sloughed tissue, which eventually improved. Even in total gland cryosurgical ablation, incontinence is seen in less than 2% of patients.[8] Incontinence, with our more minimal cryosurgical approach, would be expected to be negligible. We see this as a positive secondary effect of our attempt to improve potency, because nerve-sparing RP can have incontinence rates as high as 6%.[3]

The preservation of potency associated with nerve-sparing cryosurgery was better than we expected. Of 9 patients treated, 7 remained potent, with all potent patients satisfied with their sexual functioning. Nonetheless, this was a retrospective study, without the use of standard sexual functioning questionnaires, and investigator bias, as well as patient inclination to please the treating physician, should be considered a possible factor affecting the results reported. One patient required Viagra postoperatively to meet our success definition, and one was using Viagra preoperatively and continued its use postoperatively. In all our patients, only one NVB was spared, making these results somewhat surprising. The data on nerve-sparing RP show a significant decrease in potency rates when one NVB is spared compared with two.[2,3] Achieving high potency rates with our unilateral nerve spar-

TABLE I. *Continued*

Preoperative Hormones	Area Frozen	Postoperative PSA† (ng/mL)	PSA Stable	Biopsy Status	Change/Potency	Return to Function (mo)
No	Bilateral	0.1	Yes	Negative	Impotent	
Yes	Bilateral	0.5	Yes	Negative	Potent with Viagara	12
Yes	Bilateral	0.75	Yes	Negative	Potent	6
No	Hemi-cryosurgery	0.7	Yes	No biopsy	Potent	4
Yes	Hemi-cryosurgery	4.8	Yes	Negative	Impotent	
No	Hemi-cryosurgery	1.8	Yes	Negative	Potent	3
No	Hemi-cryosurgery	0.5	Yes	Negative	Potent	6
Yes	Hemi-cryosurgery	0.1	Yes	No biopsy, Jehovah Witness	Potent	9
No	Tumor + 1.5-cm margin	4	Yes	No biopsy, too soon	Potent	1 wk

ing, without risking a positive margin on the tumor side, is an advantage of this procedure compared with nerve-sparing RP.

These superior results for cryosurgery in unilateral nerve sparing may be explained by cryosurgery's minimal vascular disruption or the lack of nerve manipulation and trauma compared with RP.

Another difference in our results compared with those for nerve-sparing RP appears to be in the rate of potency return between the two procedures. Potency rates in nerve-sparing RP are often reported 18 months after RP. In our series, the return to function was very rapid. All patients had return to sexual functioning within 1 year of the procedure. The rapidity of return seemed, in part, related to whether the patient had been receiving preoperative hormonal therapy, as well as to the extent of freezing that was carried out.

Nerve-sparing cryosurgery seems to have advantages over brachytherapy and external beam radiotherapy, as well. Unlike brachytherapy, which is limited to patients with low-volume, low Gleason grade disease, our procedure is limited by whether the disease is confined to one side of the gland, and not to other clinical parameters. On the basis of Gleason grade, PSA levels, and extent of disease, nearly one half of the patients we treated would not have been candidates for brachytherapy alone.

Radiotherapy does not appear to maintain its initial potency advantage in the long term. Potency rates after 2 years are essentially equivalent with those after nerve-sparing RP.[15] The urinary tract complications that result after brachytherapy can have a significant effect on patient lifestyle.[16] Rectal complications, a major concern with radiotherapy, have been virtually eliminated in our procedure, by separation of the rectum and prostate with saline injection into Denonvilliers fascia before freezing. In addition, brachytherapy patients who have local failure have limited curative options available. Finally, a major drawback to radiotherapy is that patients in whom radiation fails show a significant increase in Gleason grade and tumor aggressiveness in the recurrent cancer, which adversely affects patient survival.[17] Certainly, this is not a favorable characteristic in a procedure possibly being applied to a younger patient population.

CONCLUSIONS

Our series was small and had a relatively short follow-up when considering the long clinical course of prostate cancer. If our results are eventually confirmed, however, nerve-sparing cryosurgery could have a significant impact on the treatment of prostate cancer, justifying additional investigation though a prospective multi-institutional study.

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