Salvage cryosurgical ablation of the prostate for local recurrence after radiation therapy: improved outcomes utilizing a capromab pendetide scan and biopsy algorithm

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Purpose: *We assessed the efficacy, complications and technical advancements in salvage cryosurgical ablation of the prostate for recurrent prostate cancer after radiation therapy.*

Methods: *A total of 58 patients were evaluated for salvage cryosurgery using an algorithm of capromab pendetide scan and prostate biopsy from January 2003–July 2007. Forty-seven patients underwent salvage cryosurgery and biochemical recurrence free survival and complications were retrospectively reviewed. Mean follow-up was 24 months.*

Results: *Seventy percent of patients achieved a nadir PSA < 0.5 ng/ml. Overall, 51% of patients achieved a durable PSA response with a pre-salvage serum PSA < 10 predictive of success. There were no major complications and minor complications were few.*

Conclusion: *Salvage cryotherapy in experienced hands utilizing third-generation technology provides for excellent biochemical control with minimal morbidity.*

Key Words: cryosurgery, prostatic neoplasms, capromab pendetide, prostate-specific antigen, salvage therapy

Introduction

Local recurrence of prostate cancer after definitive therapy with radiation has been reported in various series to be upwards of 30%.[1,2] The science and technology of delivering radiation has continued to improve, and most centers are recommending and safely delivering higher dose radiation to the prostate to improve success and decrease recurrence. The past 10 years, however, has seen a vast increase in the number of younger men diagnosed with prostate cancer electing to undergo brachytherapy in a desire to preserve potency and obviate a longer surgical convalescence.[3] A large portion of the patients with biochemical recurrence are likely to be younger men and the recommendations for treatment of this group of patients are also undergoing reevaluation. Previously, for biochemical recurrence after definitive radiotherapy and depending on the comorbidities, which in an older population were high, the treatments ranged from watchful waiting to hormone therapy, with salvage prostatectomy and salvage

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cryotherapy less than satisfactory alternatives. The reasons were the high rate of serious complications and low rate of disease free status after salvage therapy. Salvage prostatectomy is currently being revisited at several institutions with the rationale that in patients who fail brachytherapy, both the volume of disease as well as the radiation dose is limited in extent allowing for fewer complications and the possibility for greater disease free success rates.[4,5] Initial reports of salvage cryosurgical ablation of the prostate (CSAP) were also noted for significantly higher rates of complications than primary cryotherapy, and as a consequence this treatment often fell into disfavor.[6] Currently with the third generation cryotherapy equipment, small diameter cryotherapy needles and FDA approved urethral warming device, these complications have been greatly reduced and this therapy holds promise as a low morbidity minimally invasive treatment option for these patients.[7-9] This study reports our initial results for salvage CSAP using a third-generation argon-based system in patients referred for biochemical recurrence after definitive radiotherapy. Patients were evaluated for short and intermediate term biochemical disease free status as well as for the number and extent of complications.

Methods

Between January 2003 and July 2007 58 patients were evaluated at our institution for a rising PSA after definitive radiotherapy (external beam and/or brachytherapy) for prostate cancer in consideration of salvage CSAP. For staging, all patients underwent physical exam and capromab pendetide (ProstaScint, Cytogen Corporation, Princeton, NJ) scan to ensure they would be eligible for local-only therapy. Only patients with a negative or prostate-only positive (non-metastatic) scan were offered prostate biopsy and all patients who underwent salvage CSAP had biopsy-proven prostate cancer recurrence. Salvage CSAP was performed using the Galil Medical (Plymouth Meeting, Pennsylvania) argon-based ultra-thin 17-gauge cryoablation needles placed percutaneously through the perineum guided by a standard brachytherapy template and trans-rectal ultrasound. Eight needles, two per channel, were placed in a circumferential pattern, with two sub urethral needles. A urethral warmer was placed and freezing was initiated in an anterior to posterior fashion and monitored by trans-rectal ultrasound. Two freeze-thaw cycles were employed in all cases. Patients were discharged home the same day with an indwelling Foley catheter for 2 weeks. Follow-up consisted of a voiding trial in 2 weeks, and an assay of serum PSA values, which were obtained every 3 months for the first 2 years and every 6 months thereafter. Careful analysis of both early and late complications, as well as severity was recorded. Preoperative erectile function was assessed using the SHEM-7 questionnaire. Incontinence was considered significant if patients had to wear pads or underwent further incontinence-related medical or surgical intervention. Failure was considered an inability to reach and maintain a post-salvage PSA ≤ 0.5 ng/ml. Biochemical recurrence was considered a PSA ≥ 0.5 ng/ml and rising.

Results

Of the 58 patients evaluated, 7 patients (12%) had a metastatic Prostascint scan and were not considered candidates for salvage cryosurgical ablation. These patients were offered expectant management or hormonal therapy. The remaining 51 patients had a prostate-only or negative Prostascint scan indicating non-metastatic prostate cancer that would be amendable to local salvage therapy and underwent trans-rectal ultrasound prostate biopsy to confirm residual disease. Four patients out of the 51 (8%), had a negative prostate biopsy and were offered expectant management or hormonal therapy, leaving 47 patients who underwent salvage cryosurgical ablation, Table 1. The majority of patients were between the ages of 60-69, however 43% were older than age 70. On physical exam, all patients had a small, flat irradiated prostate. Seventy-seven percent of patients had a pre-

TABLE 1. **Pre-salvage clinical characteristics in 47 patients**

Age (years)	**%**
50-59	4
60-69	53
70-74	23
> 74	20
PSA (ng/ml)	
< 4	28
4-10	49
> 10	6
> 20	17
Gleason score	
6-7	83
8-10	17

TABLE 2. **Complications**

Event	Frequency (%)
Obstruction/bladder neck contracture	0
Rectal injury/fistula	0
Urethral slough	0
Incontinence	0
UTI	2
Gross hematuria/clot retention	4

salvage PSA < 10. The mean follow-up was 25 months (range 7-53 months). Eighty-three percent had a Gleason score of 6-7 and 17% had a Gleason score ≥ 8. Overall, 33 patients (70%) obtained a PSA nadir < 0.5 ng/ml. **N**ine patients (27%) had a biochemical recurrence post-salvage, thus 51% of patients obtained a durable post-salvage PSA nadir < 0.5 ng/ml. The mean pre-salvage PSA in the successful group was 5.35 ng/ml, compared to 12.81 ng/ml in the failure group (p = 0.009). Complications were few and considered minor, Table 2. Immediate complications included gross hematuria in two patients, requiring clot evacuation and readmission in one patient for an additional 24 hours. No patients experienced urethral sloughing, rectal fistula or urethral incontinence. Post-CSAP penoscrotal swelling and edema were minimal. No patients experienced prolonged pelvic discomfort or pain postoperatively. All patients had erectile dysfunction pre-salvage.

Discussion

Currently, the most studied options for locally recurrent prostate cancer after radiation therapy are salvage prostatectomy and salvage cryotherapy. Salvage prostatectomy initially fell into disfavor due to the high rate of complications, positive margin rate and lack of efficacy. Several centers are revisiting salvage surgery, as it may be more feasible after brachytherapy because of the more confined radiation dose and improved surgical technique, although morbidity is still high.[4,5]

Similarly, initial salvage CSAP series were looked upon unfavorably due to increased extent of freezing and the lack of an FDA approved urethral warming device. This resulted in poor biochemical control and an unacceptably high complication rate. In our series, we demonstrated superior outcomes and markedly decreased rate of complications by using third generation cryotherapy equipment, carefully selecting patients with the highest probability of local recurrence and several modifications to treatment techniques. Significant postoperative swelling and edema of the penis and scrotum reported in earlier series has been eliminated by avoiding freezing above the anterior aspect of the prostatic capsule thereby sparing the regional lymphatics. Urethral sloughing, stricture and urethral trauma have been obviated by the urethral warming catheter and careful peripheral placement of the cryo-needles to prevent urethral freezing. Similarly, careful monitoring of lethal ice progression to avoid the rectum inferiorly and the urinary sphincter apically has eliminated prostatorectal fistulas and urinary incontinence. Further modification of the equipment includes a variable length freeze to provide for more precise sculpting of the ice ball, which is ideal in short, postradiated glands.

In spite of a strict definition of success (nadir PSA < 0.5 ng/ml), our results are consistent with other published salvage cryosurgery series.[7,9] which used less strict criteria such as nadir + 2 ng/ml. Were we to adapt such criteria our efficacy would be undoubtedly better. Overall, 51% of patients achieved a post-salvage durable nadir PSA < 0.5 ng/ml. While arguably some of the nine patients who experienced biochemical recurrence post-salvage in our series may harbor occult metastatic disease,[10] we feel this number was significantly reduced by the selection of patients using capromab pendetide scanning and trans-rectal ultrasound biopsy.[11]

Conclusion

Salvage cryotherapy is an excellent treatment option for patients with proven local recurrence of their disease. Complication rates are low in the hands of an experienced cryosurgeon. It provides an opportunity for cure in patients who otherwise might only be offered palliative therapy. Patients with a pre-salvage PSA of less than ten have a significantly increased chance for long-term disease free survival. The future application of clinical stratification algorithms along with imaging may further aid in patient selection, thereby improving long term success rates.

Disclosure

Dr. Harry S. Clarke is a member of the Speakers' Bureau for Galil Medical and CryoSurgery Proctor. Dr. Thomas Keane is a member of the Speakers' Bureau for AstraZeneca, Cytogen Corporation, Auxilium Pharmaceuticals and Sanofi-Aventis. He is on the advisory board for Sanofi-Aventis and has done research for Cytogen Corporation. □

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