Long-Term Oncologic Outcomes of Salvage Cryoablation for Radio-Recurrent Prostate Cancer

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Purpose: Management of localized radio-recurrent prostate cancer is not standardized, partly due to the absence of long-term data on oncologic control and the toxicity of various treatment modalities. We analyzed the long-term oncologic outcomes and morbidity of salvage cryoablation for radio-recurrent prostate cancer.

Materials and Methods: Patients undergoing salvage cryoablation for biopsy proven, localized radio-recurrent prostate cancer from 1995 to 2004 were prospectively accrued. Preoperative characteristics, perioperative morbidity and postoperative data were reviewed from a prospectively maintained database or via telephonic contact with the patient. The primary outcome was overall survival. Secondary outcomes were metastasis-free and biochemical disease-free survival. The Kaplan-Meier method was used for survival analysis and multivariable Cox regression analysis was performed.

Results: Of 187 patients 157 (84%) had records available for followup. Mean ± SD age was 69.4 ± 5.8 years and mean presalvage prostate specific antigen was 6.6 ± 5.7 ng/ml. Median followup was 117 months (IQR 55–154). Five and 10-year overall survival was 93% and 76%, respectively. Biochemical disease-free survival at 10 and 15 years was 35% and 22.6% whereas metastasis-free survival at 10 and 15 years was 86% and 71%, respectively. On multivariable analysis precryoablation and nadir prostate specific antigen values were significant predictors of metastasis-free and biochemical disease-free survival. Age at salvage cryoablation ($p = 0.008$) and nadir prostate specific antigen ($p = 0.015$) were significant predictors of overall survival. There were 157 Clavien-Dindo grade 1-2 and 22 grade 3 complications.

Conclusions: A single center, long-term experience documented by a prospectively maintained database shows that cryoablation is a viable salvage option for radio-recurrent prostate cancer as it provides durable biochemical disease-free survival with acceptable morbidity.

Key Words: prostatic neoplasms; radiotherapy; neoplasm recurrence, local; salvage therapy; cryosurgery

Abbreviations and Acronyms

ADT = androgen deprivation therapy

BDFS = biochemical disease-free survival

CRYO = cryoablation

MFS = metastasis-free survival

PSA = prostate specific antigen

rrPC = radio-recurrent prostate cancer

RT = radiotherapy

sCRYO = salvage CRYO

SP = salvage prostatectomy

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A substantial proportion of patients with prostate cancer receive RT as the primary curative treatment.[1] At least 15% to 20% of these men will experience localized failure and may potentially benefit from salvage treatment.[2] Due to the lack of long-term data on oncologic control and

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the toxicity of various treatment modalities for salvaging rrPC the optimal treatment for this population is still undefined.

A systematic review of oncologic outcome of SP showed 70% to 83% cancer specific survival at 10 years.[3] However, SP is associated with significantly higher morbidity compared to primary radical prostatectomy.[4] Thus, a majority of men with rrPC are placed on noncurative ADT without being considered for potentially curative local salvage therapy.

We and others found that minimally invasive local ablative modalities such as CRYO can achieve reasonable intermediate term cancer control with a BDFS rate up to 70% at 5 years and acceptable treatment associated toxicity.[5–8] We analyzed the long-term oncologic outcomes and morbidity of sCRYO as documented in our prospectively maintained database.

MATERIALS AND METHODS

We prospectively recruited 187 patients with biopsy proven rrPC. Ethics review board approval was obtained for the study with extended long-term followup (REB#103538). All patients underwent abdominal and pelvic computerized tomography and radionucleotide bone scan to exclude metastatic disease. Of the patients 71% had received ADT for 3 to 6 months prior to referral for sCRYO. ADT was discontinued in all patients following the sCRYO procedure.

A total of 11 initial cases were treated with the Candela cryoablation system (Candela, Wayland, Massachusetts) and the Cryocare® system was used for the subsequent 176. Our cryoablation technique has been previously detailed.[9,10]

Preoperative clinical data, including age, PSA, Gleason score, initial clinical stage at presentation and type of radiotherapy (external beam, brachytherapy or combination), were recorded. Serial serum PSA levels were determined 3, 6, 12, 24 and 36 months postoperatively. Transrectal ultrasound guided biopsy was performed at 6, 12 and 24 months. Beyond 24 months postoperatively biopsy was performed when clinically indicated. Details of histopathological assessment of the biopsy specimens have been reported previously.[11] Patients living more than 300 km from our center were followed by respective local urologists, who were contacted for any complications and clinical sequelae.

Biochemical recurrence was defined according to the Phoenix criterion (nadir PSA +2 ng/ml).[12] Recurrence was defined as any biochemical, radiological, histological or clinical evidence of recurrent prostate cancer. MFS was defined as time from cryoablation to date of documentation of metastatic lesion(s) on imaging study. Time to the initiation of ADT was calculated from the date of cryoablation to the date of ADT prescription.

Complications were graded according to the Clavien-Dindo classification system.[13] Incontinence was defined as mild to moderate if the patient required 0 to 1 pad only and as severe if 2 or more pads were needed. Incontinence requiring surgery was defined as incontinence requiring any form of surgical intervention. Gross hematuria and perineal pain were classified under self-reported complications. Bladder neck contracture, urinary retention, urinary tract infection and fistula were physician recorded variables that were logged at scheduled followup appointments and/or extracted from hospital records.

Descriptive statistics are reported as the count and percentage as appropriate. Survival and followup are reported as the median and IQR. Survival analysis was done by the Kaplan-Meier method. Multivariable Cox proportional hazards modeling was used to assess the effects of potential covariables, including age at cryotherapy, preCRYO PSA and Gleason score, and nadir PSA. Models were generated for each outcome. The final model for each outcome included covariables that were consistently significant at $p < 0.1$ regardless of the variable entry approach. The primary outcome was OS. Secondary outcomes were MFS, BDFS and time to initiation of ADT. Morbidity is described by type of occurrence and severity according to the Clavien-Dindo schema. Statistical analyses were performed with Prism®, version 6 and SPSS®, version 20.

RESULTS

A total of 197 whole gland salvage cryoablation procedures were performed from 1994 to 2004. Ten patients underwent repeat cryoablation for persistent/recurrent disease and 157 (84%) had records available for followup. Median followup was 117 months (IQR 55–154). Table 1 lists presalvage patient characteristics.

Complete information on oncologic status/survival was available for 126 patients at 5 years, 97 at 10 years and 43 at 15 years. During this period 50 patients died, including 14 of prostate cancer and 36 of other causes. A total of 117 patients underwent repeat systematic biopsy after cryoablation. One, 2 and 5-year freedom from local recurrence rates were 95%, 90% and 73%, respectively. Overall, 27 patients (23.1%) had biopsies positive for prostate cancer with a median of 1 core positive (range 1 to 3). The most frequent site of positive biopsy was at the apex in 14 patients, followed by seminal vesicles

Table 1. *Presalvage characteristics of 187 men undergoing CRYO*

Mean ± SD age at sCRYO (range)	69.4 ± 5.8 (54–81)	
Mean ± SD ng/ml presalvage serum PSA (range)	6.6 ± 5.7 (0–36.4)	
No. presalvage Gleason score at biopsy (%):		
6 or Less	44	(23.5)
7	52	(27.8)
8–10	57	(30.5)
Undetermined	34	(18.2)
No. previous treatment (%):		
External beam RT	183	(97.8)
Brachytherapy	3	(1.6)
Combined external beam RT + brachytherapy	1	(0.53)