Extended Followup Oncologic Outcome of Randomized Trial Between Cryoablation and External Beam Therapy for Locally Advanced Prostate Cancer (T2c-T3b)

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Abbreviations and Acronyms

bDFS = biochemical disease-free survival
CaP = prostate cancer
CRYO = cryoablation
CT = computerized tomography
DSS = disease specific survival
EBRT = external beam radiotherapy
HT = hormonal therapy
LHRH = luteinizing hormone-releasing hormone
OS = overall survival
PSA = prostate specific antigen
TRUS = transrectal ultrasound

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Purpose: We assessed and compared the survival outcomes between cryoablation and external beam radiation therapy in patients with locally advanced prostate cancer (cT2c-cT3b).

Materials and Methods: Patients with locally advanced prostate cancer, recruited from 1999 to 2002, were randomized to primary cryoablation or external beam radiotherapy. All patients received neoadjuvant hormonal therapy for 3 months before and 3 months after the procedures. Patients underwent followup transrectal ultrasound guided biopsy (at 3, 6, 12, 18 and 24 months for cryoablation, and at 18 and 24 months for external beam radiotherapy) and as clinically indicated thereafter. Biochemical failure was based on the Phoenix criterion (prostate specific antigen nadir +2 ng/dl).

Results: A total of 62 patients completed the trial. Median followup was 105.2 months (SD ±35.8). Accrual was limited due to newer data favoring longer neoadjuvant hormonal therapy and higher external beam radiotherapy dose for locally advanced prostate cancer. There was a greater reduction in prostate volume in the cryoablation group after intervention (−54% vs −34%, $p \leq 0.01$). Disease specific survival and overall survival were comparable between the groups. However, the 8-year biochemical disease-free survival rate was significantly lower in the cryoablation group (17.4% vs 59.1%) ($p = 0.01$).

Conclusions: This randomized trial with median followup approaching 9 years showed that cryoablation was inferior in attaining biochemical disease-free survival in patients with locally advanced prostate cancer (cT2c-T3). Cryoablation may be more suited for less bulky prostate cancer. Longer duration neoadjuvant hormonal therapy or a multimodal approach may provide optimal biochemical disease-free survival in this patient population.

Key Words: prostatic neoplasms, cryosurgery, radiotherapy

DESPITE the widespread use of PSA as a screening modality for the early detection of prostate cancer, 20% to 35% of newly diagnosed CaP cases are still classified as high risk.[1] This includes patients with a high PSA (greater than 20 ng/dl), high Gleason score (8 or greater) or advanced local staging (T2c or greater). There is no consensus regarding the optimal treatment modality in this group of patients.[2] As monotherapy or combination treatments, options include radical prostatectomy, radiation therapy with external beam or high dose brachytherapy, ablative local treatments such as

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CRYO or high intensity focused ultrasound, or deferred treatment with surveillance and endocrine therapy.[1,3]

CRYO uses freezing to induce cell death.[4] It was initially pioneered as therapy for benign prostatic hyperplasia in the early 1960s.[5] However, it was quickly abandoned because of the high complication rate due to difficulty in monitoring the procedure and the rather primitive technology. The development of real-time monitoring with TRUS, percutaneous insertion of cryoprobes and improvement in cryogenic technology led to the resurgence of the technique in the mid 1990s.[6,7]

CRYO was then offered as primary therapy for low risk, early stage CaP and as investigational salvage therapy for radiation failure.[8–10] However, its role in locally advanced CaP was unclear.[11] In addition, the long-term outcome of CRYO in the management of CaP is lacking, especially in patients with locally advanced CaP.[12] We report the long-term outcome of a randomized trial between a standard form of therapy in patients with locally advanced CaP (EBRT) and a newer ablative therapeutic modality (CRYO).

MATERIALS AND METHODS

This randomized trial was conducted between 1999 and 2002 (fig. 1). Local ethics review board approval was obtained. Patients were considered eligible if they had a proven histological diagnosis of CaP, clinical stage T2c, T3a or T3b (AJCC Cancer Staging Manual, 5th edition)[13] based on physical examination and/or TRUS, serum PSA less than 25 ng/dl, and negative metastatic evaluation with CT and radionuclide bone scan. Patients with previous therapy (radiation or hormonal), prostate volume greater than 75 ml, metastatic or node positive disease, or American Society of Anesthesiologists risk class greater than 3 were excluded from the trial.

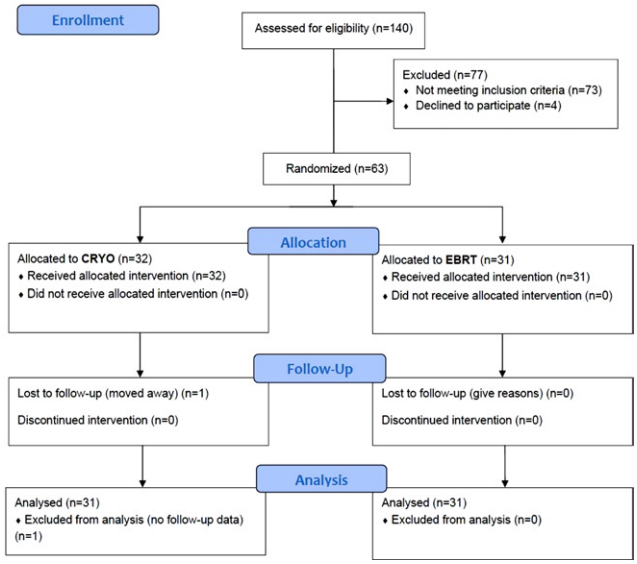

Figure 1. CONSORT flow diagram of trial

Hormonal Therapy

The standard of care at our institution for this patient cohort at the trial was short-term neoadjuvant HT[14] followed by definitive full dose external beam radiotherapy. Thus, all patients received 3 months of LHRH (goserelin), which was continued for another 3 months after the start of the actual local therapy (CRYO or EBRT). LHRH has the theoretical advantage of downsizing the prostate, especially in the CRYO arm. It is noteworthy that subsequent to the commencement of our trial, the EORTC (European Organisation for Research and Treatment of Cancer) reported a significant survival advantage for longer HT of at least 3 years.[15]

Cryoablation

The CRYO procedure was performed with the patient under general or spinal anesthesia using the Cryocare® system. All CRYO procedures were performed by 1 surgeon (JLC) who had accumulated substantial experience with CRYO therapy of the prostate since 1994.[16,17] The cryoprobes were inserted under TRUS guidance. The interprobe distance, orientation and depth of insertion were assessed with a special 3-dimensional ultrasound system developed in-house.[16] Two freeze-thaw cycles were administered and a urethral warming device (distributed by Cook Urological Inc., Spencer, Indiana) was used to protect the urethra.[7] Three thermocouple probes at the respective neurovascular bundles and in the midline apex were placed for monitoring purposes and to ensure that the required temperature of less than −40C was reached.[16,17] A trocar suprapubic catheter was inserted intraoperatively and kept open for 3 weeks. Real-time monitoring of the freezing process and progression of the ice-ball was performed with TRUS to ensure adequate therapeutic effect while safeguarding against excessive freezing.

External Beam Radiotherapy

All patients who were randomized to EBRT were treated with a standard isocentric 4-field box technique. Simulation was performed with a CT based simulator and the voltage radiotherapy equipment with photon energy of at least 10 ME was used. The standard EBRT protocol at that time consisted of 66 Gy in 33 fractions administered at 2 Gy per day, 5 days a week for a total of 6.5 weeks. The therapy was directed to include the prostate, seminal vesicles and the periprostatic region plus a 1 cm margin to account for internal organ motion and subclinical extraprostatic tumor extension.[18]

Posttreatment Followup

Posttreatment followup monitoring consisted of serum PSA every 3 months for the first year, then every 6 months in the second year followed by annual monitoring or whenever clinically indicated, and TRUS guided biopsy. Prostate volume was measured during each TRUS guided biopsy session. The frequency of biopsy was different between the arms because of the difference in anticipated therapeutic effects for the 2 arms. In the CRYO arm the therapeutic effect should be immediate, while with EBRT