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

Joseph L. Chin,*†,‡ Ali A. Al-Zahrani,†,§ Ana Maria Autran-Gomez,§ Andrew K. Williams§ and Glenn Bauman§

From the Division of Urology, Department of Surgery (JLC, AAA, AMAG, AKW), and Division of Radiation Oncology, Department of Oncology (JLC, GB), London Health Sciences Centre, University of Western Ontario, London, Ontario, Canada, and Department of Urology, Dammam University, Dammam, Saudi Arabia (AAA)

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 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. 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
CRYO or high intensity focused ultrasound, or deferred treatment with surveillance and endocrine therapy.\textsuperscript{1,3} CRYO uses freezing to induce cell death.\textsuperscript{4} It was initially pioneered as therapy for benign prostatic hyperplasia in the early 1960s.\textsuperscript{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.\textsuperscript{6,7}

CRYO was then offered as primary therapy for low risk, early stage CaP and as investigational salvage therapy for radiation failure.\textsuperscript{8–10} However, its role in locally advanced CaP was unclear.\textsuperscript{11} In addition, the long-term outcome of CRYO in the management of CaP is lacking, especially in patients with locally advanced CaP.\textsuperscript{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)\textsuperscript{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.

**Hormonal Therapy**

The standard of care at our institution for this patient cohort at the trial was short-term neoadjuvant HT\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{16,17} Two freeze-thaw cycles were administered and a urethral warming device (distributed by Cook Urological Inc., Spencer, Indiana) was used to protect the urethra.\textsuperscript{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 $-40^\circ C$ was reached.\textsuperscript{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.\textsuperscript{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...
the effect may take up to 24 months.\textsuperscript{19} For the CRYO
group biopsies were done at 3, 6, 18 and 24 months, while
in the EBRT arm they were performed at 18 and 24
months after treatment. Further biopsies were done if and
when clinically indicated. The protocol allowed the CRYO
procedure to be repeated if the first biopsy at 3 or 6 months
was positive. Such cases were not labeled as treatment
failure up to the 6-month point. Positive biopsies thereaf-
ter (at 18 and 24 months after treatment) in each arm
were classified as treatment failures and the patients
were given the option for crossover to the respective alter-
native treatment (fig. 2). The definition of biochemical
failure was based on the Phoenix criteria (second RTOG
[Radiation Treatment Oncology Group]-ASTRO [Ameri-
can Society for Therapeutic Radiology and Oncology] Con-
sensus Conference), nadir PSA +2 ng/dl.\textsuperscript{20}

The primary end points of the trial included overall
survival and DSS. The secondary outcomes were bDFS
and clinical progression. Statistical analysis was per-
formed using commercially available software (SPSS®
version 17). The unpaired t test (parametric variables)
and Mann-Whitney test (nonparametric variables) were
used. The categorical variables were analyzed with the
Fisher exact test. DSS, OS and bDFS curves were esti-
imated using the Kaplan-Meier technique. Statistical sig-
ificance was set at \(p < 0.05\) and was 2-sided.

RESULTS

In all, 62 patients completed the trial and median
followup was 105 months. There were 22 patients
(35.5\%) who had a followup of more than 10 years.
Accrual to the trial slowed considerably after the
EORTC report of superior results with a longer du-
ration of adjuvant endocrine therapy with EBRT for
this patient population.\textsuperscript{15} Therefore, the decision
was made to terminate the trial. Table 1 summa-
izes patient demographics and clinicopathological
characteristics. Median prostate volume before ther-
apy as measured by TRUS was smaller in the CRYO
arm (31.3 vs 40.9 ml, \(p = 0.03\)). There was no dif-
ference in age, PSA, Gleason score, clinical stage,
number or locality of the positive needle biopsies be-
tween the arms. Both treatment modalities induced a
reduction in prostate volume with a greater reduction
in the CRYO arm (\(-54\% \text{ vs } -36\%\), \(p = 0.01\)).

There was no statistical difference in the number of
positive prostate biopsies after treatment (22.6\% in
the CRYO group and 19.4\% in the EBRT group)
nor the time to positive biopsy, with the majority of
the positive biopsies documented within the first 3
years of followup. Distant metastasis developed in 2
(6.5\%) patients in the CRYO arm vs 3 (9.7\%) in the
EBRT arm.

Hormonal therapy was commenced in 11 patients
in the CRYO arm (35.5\%) vs 5 (16.1\%) in the EBRT
arm (\(p = 0.002\)) due to biochemical failure and/or
clinical progression. DSS and OS were comparable
between the 2 arms (table 2). However, bDFS was
significantly lower in the CRYO arm (17.4\% vs
59.1\%, \(p = 0.01\)) and mean time to biochemical fail-
ure was shorter (28 vs 41 months, \(p = 0.01\)) com-
pared to the EBRT group (fig. 3). Adverse events had
been reported previously and were not the primary
purpose of this report. Since the previous report\textsuperscript{12}

\begin{table}
\centering
\caption{Patient and tumor characteristics}
\begin{tabular}{lccc}
\hline
 & All & CRYO & EBRT & \(p\) Value \\
\hline
No. pts & 62 & 31 & 31 & \\
Median ± SD age & 70.6 ± 5.8 & 70.4 ± 5.5 & 70.5 ± 6.2 & Not significant \\
Median ± SD ng/ml PSA & 9.9 ± 6.8 & 11.1 ± 6.8 & 8.6 ± 6.5 & Not significant \\
No. Gleason score: & & & & Not significant \\
4-6 & 3 & 2 & 1 & \\
7 & 48 & 24 & 24 & \\
8-10 & 11 & 5 & 6 & \\
No. tumor stage: & & & & Not significant \\
T2c & 20 & 12 & 8 & \\
T3a & 32 & 17 & 15 & \\
T3b & 10 & 2 & 8 & \\
Median ± SD ml prostate vol & 35.6 ± 14.8 & 31.3 ± 16.8 & 40.9 ± 11.3 & 0.03* \\
No. pos biopsy at & & & & Not significant \\
diagnosis: & & & & \\
2 or Less & 19 & 9 & 10 & \\
3 & 21 & 13 & 8 & \\
4 or Greater & 22 & 9 & 13 & \\
No. locality of prostate Ca: & & & & Not significant \\
Unilat & 36 & 18 & 18 & \\
Bilat & 26 & 13 & 13 & \\
Median ± SD mos followup & 105.2 ± 35.8 & 101.5 ± 30.9 & 113 ± 40.4 & Not significant \\
\hline
\end{tabular}
\end{table}

\* Mann-Whitney U test.
there had been no long-term adverse sequelae directly attributable to either procedure.

**DISCUSSION**

The proposed mechanisms of cell kill for CRYO include, among others, dehydration, direct cell membrane rupture, vascular microthrombosis and apoptosis. Theoretically, this technique has the advantage of being cytocidal for prostate cells regardless of the endocrine response status and the freezing can be extended to periprostatic tissue. The latter feature is particularly important in patients with locally advanced prostate cancer (cT2c or greater). However, the clinical efficacy and long-term oncologic outcomes of CRYO in this group of patients have been disappointingly suboptimal. The use of CRYO for CaP has been approved by the American Urological Association and the European Association of Urology, while the United Kingdom National Institute for Health and Clinical Excellence recommends the procedure only in a clinical trial setting. Our trial was designed in the mid 1990s to compare the oncologic outcome between CRYO and EBRT for locally advanced CaP. Short-term neoadjuvant LHRH therapy along with EBRT was the standard of care when the trial was designed. For the CRYO group neoadjuvant LHRH therapy would theoretically help in downsizing the prostate and increasing the likelihood of coverage of the entire prostate by the cryoablative process. The EORTC trial by Bolla et al showed a survival benefit with a longer duration of hormonal therapy (3 years) and higher radiation doses (79 Gy) in patients with locally advanced CaP. This information had a significant negative impact on the accrual of our study. Since altering the protocol midstream would have rendered the results uninterpretable, we elected to close the trial with fewer patients than originally planned. Nevertheless, this trial remained one of a few randomized studies comparing 2 interventional modalities for prostate cancer. The long-term results showed a favorable outcome for EBRT compared to CRYO even with lower radiation treatment doses than are currently used.

Our trial has several limitations. It is a single center report with a small number of subjects because of the premature accrual closure. The strengths of our trial include that it was a prospective randomized study conducted at a single site with uniform treatment practices. It was also the only randomized trial to our knowledge in patients with locally advanced CaP against standard therapy (EBRT). Another strength was the longer term followup approaching 9 years.

With followup close to 9 years, only 17% of the CRYO group had bDFS vs 59% of the EBRT group using the Phoenix criteria for the definition of biochemical failure. With serial postoperative TRUS (prostate size measurement and biopsy), the CRYO group showed greater percentage decreases in prostate size than the EBRT cohort (−54% vs −36%), although the CRYO group had a lower median pretreatment volume. Although real-time monitoring improved our ability to control the extent of tissue ablation with CRYO, overzealous extracapsular freezing would still increase the risk of injury to adjacent vital structures (ie rectum, bladder, external sphincter and ureters), especially in patients with locally advanced and bulky disease. Thus, the surgeon tended to err on the cautious side in averting fistula formation and incontinence. Thus, there was a likelihood of undertreatment which consequently might have compromised the cancer ablative effect.

One of the safety features of CRYO is protection of the urethra with a warmer to minimize urethral sloughing and stricture formation. We had the benefit of a commercial warming device (approved in

<table>
<thead>
<tr>
<th>Prostate vol reduction (%)</th>
<th>−54</th>
<th>−36</th>
<th>0.01*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. pos biopsy (%)</td>
<td>7 (22.6)</td>
<td>6 (19.4)</td>
<td>Not significant</td>
</tr>
<tr>
<td>Mean mos to pos biopsy</td>
<td>37.7</td>
<td>43</td>
<td>Not significant</td>
</tr>
<tr>
<td>Mean mos bDFS</td>
<td>28</td>
<td>41</td>
<td>0.01*</td>
</tr>
<tr>
<td>8-Yr bDFS (%)</td>
<td>17.4</td>
<td>59.1</td>
<td>0.011</td>
</tr>
<tr>
<td>8-Yr DSS (%)</td>
<td>64</td>
<td>69</td>
<td>Not significant</td>
</tr>
<tr>
<td>8-Yr OS (%)</td>
<td>60</td>
<td>62.1</td>
<td>Not significant</td>
</tr>
</tbody>
</table>

* Mann-Whitney U test.
† Fisher’s exact test.

Figure 3. Kaplan-Meier curve for bDFS of EBRT vs CRYO.
Canada) which might have minimized urethral morbidity. Leibovich et al found that most patients with prostate cancer in close proximity to the urethra had locally advanced disease. In addition, depending on the contour and shape of the prostate, there might be zones of incomplete therapy in the prostate at the periphery or between the cryoprobes. Possible explanations for the discrepancies between higher biochemical failure differences and the positive biopsy rate between CRYO and EBRT include preservation of normal prostate tissue in the perirethral tissue in the CRYO group, a greater likelihood of inadequate ablation of the peripheral tissue, as yet undetected occult metastatic disease, or a combination of these factors. Of note, Donnelly et al reported a significantly lower positive biopsy rate in patients treated with CRYO with more localized disease compared to EBRT (7.7% vs 28.9%) in their randomized trial, albeit with a different study population and protocol. A difference in the extent of freeze between the 2 protocols might have also contributed to a difference in the results of the 2 randomized trials.

In contrast to bDFS, DSS and OS were comparable between the 2 groups in our study. It was difficult to compare the CRYO result with the previously reported outcomes. Most of these reports had a combination of localized and more advanced cases. Moreover risk categories rather than tumor stage were typically used in these studies, often with a preponderance of lower risk cases. Only 12% to 20% of the patients in these studies were classified as high risk and the use of HT was not clearly documented in most series. Prepelica et al reported 83.3% bDFS in 65 cases classified as high risk CaP (PSA 10 ng/dl or greater, Gleason 8 or greater). However, the biochemical definition was based on the ASTRO criteria and median followup was short (3 years). Cohen et al reported the 10-year bDFS in their high risk group (2 or more of the factors PSA 20 ng/dl or greater, Gleason 8 or greater, or T stage T3 or greater) to be 45.5%.

The long-term followup of our patients showed clearly lower bDFS in the CRYO group compared to the EBRT counterpart. These results should not be extrapolated to patients with more localized disease. In the randomized trial of CRYO vs EBRT in patients with localized CaP by Donnelly et al, OS and DSS were comparable. In the CRYO group there was a trend toward higher bDFS and the rate of positive biopsy was significantly lower. Our results would suggest that monotherapy with CRYO in patients with locally advanced CaP is a suboptimal treatment.

CONCLUSIONS

This randomized trial showed that CRYO was inferior in attaining bDFS with close to 9 years of followup in patients with locally advanced CaP (cT2c-cT3). As shown by others, CRYO may be more suited for less locally advanced CaP. Longer duration neoadjuvant HT or a multimodality approach should be evaluated to see if it can provide better bDFS for this patient group.

REFERENCES


