Cryosurgery for Prostate Cancer—Experience with Third-Generation Cryosurgery and Novel Developments in the Field

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1. Introduction

Prostate cancer is a common cancer with a significant morbidity and mortality. The advent of prostate-specific antigen (PSA) has led to an increase in the diagnosis of localised and locally advanced prostate cancer, making the condition potentially curable. The standard treatment of prostate cancer has been radical prostatectomy or radical external beam radiotherapy (EBRT) for a few decades now [1]. Brachytherapy has also established its place in the management of localised...
prostate cancer with good results [2]. Radical treatments such as surgery and radiotherapy have a significant morbidity associated with them, prompting a move towards less invasive procedures with lower morbidity.

More recently prostate cryosurgery has been used in the management of prostate cancer as a primary treatment for localised disease or as a salvage treatment for radiation failures, both EBRT and brachytherapy [3,4]. Prostate cryosurgery has undergone a number of changes over the last four decades, aiming to improve the safety and reproducibility of the procedure. From the development of 17-G cryoneedles and the use of argon gas as the freezing agent to the use of transrectal ultrasound (TRUS) guidance, urethral warming catheters, and freezing agent to the use of transrectal ultrasound (TRUS) guidance, urethral warming catheters, and temperature-monitoring probes, all have made the procedure safer and more reproducible [5–8]. Further developments continue in the field with the more recent introduction of IceRods™, a 17-G cryoneedle with an advanced heat exchanger over two points per needle, with the ability to form a larger ice ball and reach lower temperatures during a treatment cycle than the conventional cryoneedles. Also, the development of Multitemp™ 1601 temperature-monitoring probes with the ability to monitor temperatures at four or eight points per probe in real time is promising.

In our centre, prostate cryosurgery has been carried out for the last 3 yr. Here, we present the data on our experience with cryosurgery.

2. Methods

Between August 2003 and November 2006, a total of 91 patients with prostate cancer underwent prostate cryosurgery. Forty-nine patients had the treatment as a primary procedure, and 42 patients had the treatment as a salvage treatment for radiation failure: 32 post-EBRT and 10 postbrachytherapy. All patients had biopsy-proven prostate adenocarcinoma, negative magnetic resonance imaging, and negative bone scans. Other pretreatment assessments included PSA levels, sexual potency, and an International Prostate Symptom Score (IPSS). For prostate volumes larger than 50 cc, pretreatment hormonal therapy with an antiandrogen, usually bicalutamide 150 mg once a day for 3 mo, was given to downsize the gland. We used a standardised protocol in our centre. All patients had a suprapubic catheter (SPC) placed under cystoscopy guidance. The cryoneedles were placed under TRUS guidance so as to ensure adequate treatment of the entire gland. The type of needles used depended on the length of the prostate, with SeedNet™ needles used for prostates shorter than 3.5 cm and IceRods™ for prostates longer than 3.5 cm. These were placed under TRUS guidance. We used two single-point temperature-monitoring probes, one in the prostate substance and a second in the external urinary sphincter. Additionally for the first 71 cases, two temperature probes were placed in the region of the neurovascular bundles and one in the rectoprostatic space. In the last 20 cases we used a reusable multiple-point Multitemp™ temperature-monitoring probe, which can record temperatures in a continuum of either four points, at 10-mm intervals, or eight points, at 5-mm intervals. This probe is based on Bragg grating fibre optic technology and is inserted though a disposable sheath of a 17-G calibre. We placed two four-point temperature-monitoring system (TMS) 1601 probes just outside the prostate near the neurovascular bundles. One eight-point TMS 1601 was placed in the rectoprostatic space in the midline. A flexible cystoscopy was then carried out to ensure that the cryoneedles or probes were not transecting the urethra. If so, these were replaced. Finally a urethral-warming catheter was placed with warm fluid circulating through it at a temperature of 40 °C. Two cycles of rapid freeze-thaw was then carried out, ensuring the temperature in the prostate and just outside it was below a therapeutic value of −40 °C. Care was taken to ensure the temperatures in the rectum and external urinary sphincter did not go below 0 °C. At the end of the procedure, the needles and probes were removed and pressure applied to the perineal area for 10 min to reduce bruising. The urethral-warming catheter was removed 30 min after completion of the procedure. The SPC was removed after 2 wk.

The patients were reviewed at 6 wk, and 3, 6, 9, 12, 18, 24, 30, and 36 mo, at which times a PSA level was checked, sexual potency and urinary symptoms assessed, and IPSS questionnaire completed. Repeat biopsies were undertaken if the PSA levels were rising.

3. Results

A total of 91 patients underwent prostate cryosurgery as a primary (n = 49) or salvage treatment (n = 42) for radiation failures (EBRT: 32; brachytherapy: 10). The mean age of the patients undergoing primary treatment was 63.7 yr (range: 45–76). The mean PSA at diagnosis was 14.6 ng/ml (range: 2.2–48.2). For the salvage group, the mean age of the patients was 60.48 yr (range: 48–70) for patients having had EBRT as a primary treatment and 60.55 yr (range: 52–68) for patients having had brachytherapy as a primary treatment. The mean PSA precryother-

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<th>Table 1 – Patient data for all 91 patients, depicting age demographics and PSA at diagnosis (prior to cryosurgery)</th>
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<td>No. of patients</td>
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PSA = prostate-specific antigen; EBRT = external beam radiotherapy.
apy in the salvage group was 31.55 ng/ml (range: 2.2–85) for patients who had EBRT as a primary treatment and 13.5 ng/ml (range: 4.8–32.2) for patients who had brachytherapy as a primary treatment (Table 1).

The PSA readings postcryotherapy were assessed for all three groups separately and plotted over 2 or 3 yr. For the primary group, at the 6-mo follow-up, 25 of 39 patients had a PSA < 0.5 ng/ml. Further analysis revealed a group of patients with detectable but low PSA levels who had stable disease over the time scale assessed. The number of patients with PSA levels below 1 and 2 ng/ml are shown in the graph (Fig. 1). Similarly, we assessed the PSA readings of the patients in the salvage cryotherapy group, looking at previous EBRT and brachytherapy patients separately (Figs. 2 and 3).

Impotence rates were high as expected. In the primary group, of 33 patients assessed at 1 yr 9 were still sexually potent, 5 with the help of phosphodiesterase (type) 5 (PDE5) inhibitors. In the salvage group, for previous EBRT, all patients were impotent and, for previous brachytherapy, 1 of 5 patients assessed at 1 yr had partial erections with the help of PDE5 inhibitors.

Major complications included three rectourethral fistulas, all occurring in the salvage group: one for previous EBRT and two for previous brachytherapy.

4. Discussion

Over the last two decades, a number of changes have been noted in the field of prostate cryosurgery, all
endeavouring to improve the oncologic outcome whilst simultaneously reducing the morbidity associated with the procedure [5–8]. As a primary treatment, prostate cryosurgery is promising with short-term results comparable to the more conventional treatments such as radical prostatectomy, radical EBRT, and brachytherapy [3,4]. Oncologic outcomes much depend on good patient selection along with accurate monitoring of temperatures reached within and just outside the prostate. TRUS plays a crucial role in optimal placement of cryoneedles and temperature-monitoring probes [8]. Its use in the monitoring of treatment during the freeze–thaw cycles is limited by the fact that 99% of the acoustic waves are reflected by the advancing iceball front [9]. None the less, as far as protecting the rectum from cryogenic injury and subsequent fistula formation, TRUS along with the temperature-monitoring probe placed in the rectoprostatic space ensures minimal damage to the rectum. In salvage treatment, however, this procedure can be more difficult because of previous radiation damage to the tissues in the area and also, particularly with previous brachytherapy treatment, because of the seeds within the prostate scattering the ultrasound waves, thus distorting the TRUS image, and making needle and temperature probe placement more difficult than for primary or EBRT failure patients. An additional finding is rectal tenting at the apex of the prostate, which we have noted in all cases of

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Fig. 3 – Graph showing the prostate-specific antigen (PSA) readings over a 2-yr period after cryotherapy in patients previously treated with brachytherapy.

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Fig. 4 – Transrectal ultrasound image of prostate cryosurgery depicting the tenting of the rectal wall near the prostatic apex. (Multitemp™ temperature-monitoring system [TMS] 1601.)
primary treatment, is exaggerated after radiation treatment, and, in turn, would make this area more prone to cryogenic damage (Fig. 4). Conventional temperature-monitoring probes have the ability to monitor the temperature in a single point along the rectoprostatic space and so would not routinely monitor the temperatures near the apex. All three rectourethral fistulas in our series occurred in radiation-failed salvage treatments at the prostatic apex. This is an area that requires further research. A better understanding of dosimetry curves, radiation-induced tissue damage, and replication of the “tenting” effect of the rectum at the prostate apex needs to be addressed.

Since temperatures reached during freezing are crucial to achieve adequate cellular damage, it is vital that temperatures are monitored as accurately as possible [10,11]. We used a novel temperature-monitoring system for the last 20 cases. The Multi-temp™ 1601 temperature-monitoring system is a reusable fibre optic probe placed through a 17-G disposable plastic sheath, which can measure temperatures at four or eight points along a line. We used the eight-point probe to measure the rectoprostatic space. This probe covered a 4-cm length and routinely would measure the temperature near the prostatic apex, allowing more accurate measurement of temperatures in the area with the aim of minimising tissue damage and subsequent fistula formation.

Another development with use in prostate cryosurgery is IceRods™. These are cryoneedles with an advanced heat exchanger capable of forming iceballs of over 6 cm in length and able to reach temperatures below −40 °C in a shorter period of time compared with the conventional cryoneedles. These cryoneedles, in our opinion, are useful in larger glands with lengths in excess of 3.5 cm. With the conventional cryoneedles, a pullback technique followed by a repeat of the two freeze–thaw cycles would be required, lengthening the procedure with a potential to increase the associated morbidity.

Our data on 91 consecutive patients treated with prostate cryosurgery, including 49 patients treated primarily and 42 as a salvage for radiation failures, are encouraging. We found that, in all three groups, more than two thirds of patients had PSA levels either undetectable (ie, <0.5 ng/ml) or <2 ng/ml as a stable figure. Throughout the period assessed, there was a constant group of patients whose PSA levels did not drop to <0.5 ng/ml but none the less remained stable at <2 ng/ml for the period assessed. This trend was noted in all three groups.

There were three cases of rectourethral fistulas, all occurring in the salvage group, two having had EBRT and two brachytherapy. These fistulas occurred at the level of the prostatic apex, emphasising the need to monitor the temperature more closely in this area. Impotency rates were high as expected, with only 4 of 32 patients sexually potent and an additional 5 sexually potent with the help of PDE5 inhibitors. In the salvage group only 1 of 23 patients had partial erections with the help of PDE5 inhibitors.

5. Conclusions

Prostate cryotherapy has evolved over the last few decades and, in its current form, offers the potential of becoming a curative treatment for localised and perhaps locally advanced prostate adenocarcinoma. Recent developments have aimed to make the procedure safer and more reproducible, simultaneously allowing keen clinicians to learn the technique in a shorter period of time. Further developments and research are needed in the patient selection criteria, temperature-monitoring probes, and a better understanding of rectal injury, all of which will improve oncologic outcomes without compromising patient safety.

References