Cryotherapy for the prostate: an in vitro and clinical study of two new developments; advanced cryoneedles and a temperature monitoring system

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OBJECTIVES
To assess the characteristics of two new developments in cryotherapy for the prostate, IceRods™ (Oncura, Amersham, UK; 17 G cryoneedles with an advanced heat exchanger which produces a precise ice-ball comparable in size to those with larger diameter cryoneedles) and the Multitemp™ 1601 temperature monitoring system (TMS, InvivoSense, Trondheim, Norway) probes, in an in vitro model and in a clinical setting, to assess their usefulness, focusing in particular on the TMS probes.

PATIENTS, MATERIALS AND METHODS
We assessed the temperature profile and performance of the IceRods in several different configurations, in conjunction with the TMS probes for temperature mapping, in a phantom prostate model. Subsequently 20 patients with prostate cancer were treated with cryosurgery either as a primary or secondary treatment for radiation failure; all had a standard treatment protocol. The temperatures throughout the procedure were recorded accurately and analysed.

RESULTS
The IceRods were better able to freeze tissue, reaching lower temperatures than conventional cryoneedles. The IceRods were also capable of forming ice-balls with a maximum diameter of >6 cm after freezing at full power for 10 min. The TMS probes depicted real-time temperature gradients over either four or eight points in a linear array, enabling more thorough monitoring of the temperature changes during a treatment cycle. In the clinical setting, in all 20 patients, therapeutic freezing of <−40 °C was achieved in both the cycles. Temperatures of ≈ −40 °C were attained in the area just outside the prostate, as measured by the TMS probes, but with variation along the longitudinal axis. The rectal and external urinary sphincter temperatures did not fall below 0 °C at any of the points along the eight-point temperature probe, but there was variation in temperature along the prostate.

INTRODUCTION
Prostate cancer has a high incidence worldwide, being the commonest cancer affecting men in the UK and second commonest cancer affecting men in the USA. It also has the second highest cancer-related mortality in the UK and the third highest in the USA (data from Cancer Research UK and American Cancer Society online publications). The advent of PSA testing has changed the profile of prostate cancer, with more cases being diagnosed at an earlier stage, thus making them amenable to curative procedures. Although much debate still exists about the ‘best’ or ‘gold standard’ treatment for prostate cancer, radical prostatectomy and radical radiotherapy have become standard treatments for managing prostate cancer. However, these two treatment options have significant morbidity associated with them. The search for alternative therapeutic options with lower morbidity and better patient acceptance led to the introduction of brachytherapy, cryotherapy and high intensity focused ultrasound.

Cryotherapy for the prostate was first used as a therapeutic procedure in the 1960s by Soanes and Gonder [1] and Gonder et al. [2], who described an open perineal approach to the prostate, followed by cryoaablation. Not surprisingly, the morbidity of the procedure was high, making the procedure unpopular with clinicians at the time. The advent of TRUS brought about a resurgence of cryosurgery [3,4]. This was followed by constant technical development of the procedure, the main areas being the type of freezing agent used, the cryoneedles, the use of a urethral warming catheter and temperature monitoring probes (TMPs) [5,6]. Initially the freezing agent used was liquid nitrogen, which required large-calibre probes. This was replaced with argon gas, which could be delivered through smaller calibre probes and more recently using ultrafine 17 G needles, with an expected reduction in needle-related morbidity. Helium gas is used as the active thawing agent. The older cryoneedles can form a single ice-ball per needle, due to the presence of a single

CONCLUSION
IceRods and the TMS probes are clinically useful, requiring fewer cryoneedles and with more efficient temperature monitoring; this would be expected to reduce morbidity and increase safety without compromising an adequate oncological outcome. The IceRods were useful in larger prostates of >3.5 cm long, which obviated the need for a ‘pull-back’ technique. The TMS probes showed convincingly the variation in temperatures along one line, suggesting that single-point temperature monitoring might not accurately depict the lowest temperatures reached during treatment, which is particularly important in the rectum. This is a significant development in cryosurgery and would make the procedure safer, reproducible and allow interested clinicians to learn the technique safely and more quickly.

KEYWORDS
prostate cancer, cryotherapy, cryoneedles, temperature monitoring probes
heat exchanger. The individual ice-balls fuse to form a larger ice-ball with a maximum diameter of ≈ 4 cm after 10 min of freezing. The limitation in the size of the ice-ball was evident in larger prostates, where a ‘pull-back’ technique, followed by a repeat of the freeze-thaw cycles, had to be adopted, lengthening the procedure time.

Single-point TMPs were developed using the principle of the thermocouple, where different metal thermocouples (T type) provide a single heat exchanger in the tip of the probe to monitor the temperatures achieved in the prostate and surrounding tissues. With a better understanding of the mechanisms of cryotherapy-induced cell death, the need to accurately measure the temperatures has become evident [7–9]. TRUS has the limitation that up to 99% of the acoustic waves are reflected from the surface of the ice-ball closest to the TRUS probe, making it impossible to assess the adequacy of freezing during the procedure. Also, TRUS gives the surgeon no reliable data on the temperatures reached [10]. TMPs in current use are the same size as the cryoneedles and up to five TMPs are used per treatment, i.e. one in the prostate tissue, one each outside the prostate near the neurovascular bundles bilaterally, one anterior to the rectum and one in the external urinary sphincter, all placed under TRUS control. This allows the surgeon to monitor the temperature, ensure adequate freezing in the prostate extending up to the neurovascular bundles, but preventing low temperatures in the sphincter and rectum. To further protect the rectum additional cryoneedles can be placed anterior to the rectum to actively thaw the area if needed. The most appropriate placement of the cryoneedles and TMPs is still debated and tends to rely on the surgeon’s experience. The number of cryoneedles used depends largely on the size and shape of the prostate as determined by TRUS. The placement of the TMPs is vital and with only single points of temperature measurement, information on the adequacy of freezing can be misleading, as they do not measure the continuum of the temperature.

More recently, there have been two notable developments in TMPs and cryoneedles. A re-usable multiple-point temperature monitoring system (TMS, Multitemp™ 1601, InvivoSense, Trondheim, Norway) was developed which can record temperatures in a continuum of either four points at 10-mm intervals, or eight points at 5-mm intervals. The TMS is based on Bragg grating fibre-optic technology and is inserted though a disposable 17 G sheath. The main advantage of this system is to measure temperatures at various points in a longitudinal axis, which will allow the surgeon a better assessment of the adequacy of treatment. New cryoneedles (IceRods™, Oncura, Amersham, Bucks, UK) have been developed which have an advanced heat exchanger with an extended area of heat exchange, resulting in a precise ice-ball that is comparable in size to that with larger diameter cryoneedles [11]. The expected result is a larger ice-ball at lower temperatures.

Here we describe our in vitro assessment of these two developments, aimed to give a better understanding of their usefulness in the clinical setting. We subsequently tested these two developments in the clinical setting, focusing more on the TMS probes, particularly for rectal temperature monitoring.

PATIENTS, MATERIALS AND METHODS

Disposable phantom prostates were used for all the experiments (CIRS tissue simulation and phantom technology, Virginia, USA). IceRods and SeedNet™ (for use with the SeedNet cryotherapy system) were kindly provided by Oncura, and the Multitemp 1601 TMS was kindly provided by InvivoSense. With the TMS probes, disposable 17 G sheaths and the opto-electronic interrogation unit (which converts wavelength information to temperature readings) were provided by InvivoSense. The data were displayed on a computer as real-time readings in linear graphs, providing storable data.

In all there were four experiments; in the first, the effect was assessed of a single freeze-thaw cycle of one IceRod on the TMS probes placed at various distances. In the second the combination of four IceRods was used to create a larger ice-ball and the effects of a single freeze-thaw cycle on the TMS probes at various locations were plotted. In the third IceRods were placed in a clinical configuration and the effect of a single freeze-thaw cycle was assessed on TMS probes. In the final experiment, SeedNet needles were used in a clinical configuration and the effects of the freeze-thaw cycles were assessed on the TMS probes.

**TABLE 1 The distribution of the 20 patients amongst primary and secondary treatments**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary treatments</td>
<td>10</td>
</tr>
<tr>
<td>Brachytherapy failures</td>
<td>3</td>
</tr>
<tr>
<td>Radiotherapy failures</td>
<td>6</td>
</tr>
<tr>
<td>Cryotherapy failures</td>
<td>1</td>
</tr>
</tbody>
</table>

**Experiment 1:** One IceRod was used with three TMS probes (two four-sensor and one eight-sensor). The IceRod was placed centrally in the phantom prostate and the TMS probes were placed at 5, 10 and 15 mm from it. On freeze-thaw cycle was used and the temperature recorded and analysed. The IceRod was pre-tested and 100% argon flow applied for 10 min. The experiment was repeated after retracting one four-point TMS probe and retracting the second four-point TMS probe to assess the length of prostate at subzero temperatures.

**Experiment 2:** Four IceRods were placed in a square configuration 10 mm apart and the TMS probes placed at three different distances from the IceRods. One freeze-thaw cycle was used and temperatures recorded and analysed. The IceRods were pre-tested and 100% argon flow applied for 10 min.

**Experiment 3:** A standard configuration of eight IceRods, similar to that in a clinical setting, was placed in the phantom prostate (two anteriorly, two in the middle and four posteriorly). The two four-sensor TMS probes were placed laterally just outside the prostate and the eight-sensor probe posteriorly just outside the prostate. One freeze-thaw cycle was used and the temperatures recorded and analysed. Freezing was conducted as in the clinical setting, with the anterior cryoneedles being frozen first, followed by the posterior ones. A total freezing time of 15 min was used.

**Experiment 4:** The 12 SeedNet needles were placed in the prostate in a conventional pattern of four anteriorly, four in the middle and four posteriorly. TMS probes were placed with two four-sensor probes laterally just outside the prostate and an eight-sensor probe posteriorly outside the prostate; temperatures were recorded and analysed, with one freeze-thaw cycle. Freezing was continued for 10 min. In all experiments, the
FIG. 1.

(a) The three TMS probes (two four-point, red and yellow; and one eight-point, blue) were placed at 5, 10 and 15 mm from a single IceRod needle (black). The temperature readings are depicted as area graphs and three-dimensional plots of temperature vs time.

(b) Schematic representation of the TMS probe placement in relation to the IceRod (black). The TMS probes are red and yellow for the four-point probes and blue for the eight-point probe. (c) A line graph representing the temperature readings from all 16 points of the three TMS probes used as shown in (b). Line graphs 0 and 1 represent the temperature readings of the distal-most point of the red probe and proximal-most point of the yellow probe.
ambient temperature of the new disposable phantom prostate before starting treatment was 24 °C.

For the clinical testing, over a 6-month period, 20 patients with prostate cancer (either localized or locally advanced but not metastatic) were treated with cryosurgery either as a primary treatment or a secondary treatment in those in whom radical external beam radiotherapy or brachytherapy had failed (Table 1). All patients (mean age 66.1 years, range 54–73; PSA nadir 13.07 ng/mL, range 3.8–45) were staged, and had TRUS and biopsies of the prostate, a bone scan and MRI.

We used a standardized protocol; all patients had a suprapubic catheter placed under cystoscopic guidance, and the cryoneedles were placed under TRUS guidance. The type of needles used depended on the length of the prostate, with SeedNet needles used for prostates of <3.5 cm and IceRods for those >3.5 cm. SeedNet needles have one heat exchanger per needle and therefore form a single ice-ball per needle, the maximum diameter being 3.5 cm after 10 min of freezing. IceRods can form two ice-balls per needle, resulting in an ice-ball of 6 cm in maximum diameter after 10 min of freezing. The number of needles needed was determined by the type of needle used, with an average of 12 SeedNet needles or eight IceRod needles per treatment. We used two single-point TMPs, one placed within the prostate and a second in the external urinary sphincter. We placed two four-point TMS probes just outside the prostate near the urethral if so, they were removed and blunt pressure applied to ensure that the cryoneedles or probes were midline. Flexible cystoscopy was then used to create a larger ice-ball (Fig. 2). Subzero temperatures were recorded in all sensing points on all TMS probes. The probe nearest to the IceRods (yellow) recorded −75 °C, while that in the centre of the square (blue) recorded −62 °C, and the probe outside the square (red), −35 °C, while the temperature of prostate at subzero temperatures was 2 cm after 10 min of freezing (Fig. 2).

In experiment 3, with an eight IceRod configuration as shown in the graph, the temperature in the two four-sensor probes (red and yellow) decreased to therapeutic levels, i.e. <=−40 °C, while the rectal probe (blue) recorded −5 °C (Fig. 3).

In experiment 4, with the SeedNet needles, the lowest temperature reached was −40 °C for the probes within the prostate (yellow and red), whilst the rectal probe (blue) recorded −5 °C (Fig. 4).

On clinical testing, the lowest temperature reached in the prostate was −40 °C to −60 °C, as recorded by the single-point TMP in both cycles (Fig. 5). The lowest temperatures in the three TMS probes varied depending on the distance from the tip of the probe (Fig. 6). The temperature in the external urinary sphincter did not fall below 0 °C at any point through the two cycles (data not shown). The temperature in the rectal area

FIG. 2. A, a schematic representation of the placement of the IceRods (black) and TMS probes (red, yellow and blue). B, C and D are temperature readings of red, yellow and blue probes, respectively, depicted as an area graph below with corresponding interpolation graphs above.
FIG. 3. A, a schematic representation of the placement of the IceRods (black) and TMS probes (red, yellow and blue). B, C and D are temperature readings of the red, yellow and blue probes, respectively, for a single cycle of freeze-thaw on the right, with an interpolation graph of the same readings on the left.
FIG. 4.
A, a schematic representation of the SeedNet needle placement (black) and TMS probes (red, yellow and blue). B, C and D are temperature readings of the red, yellow and blue probes, respectively, for a single cycle of freeze-thaw on the right with an interpolation graph of the same readings on the left.
The mean temperature reached in various parts of the prostate to guide the adequacy of the treatment. TMPs in current clinical use measure the temperature at one point, and thus the reading depends entirely on the position of the probe, which can potentially be misleading. Probes too close to a cryoneedle would give a falsely reassuring low temperature reading, whilst a probe not measuring the lowest temperature can falsely reassure the surgeon about the safety in regions where a low temperature is associated with morbidity, e.g. the rectum and the external urinary sphincter.

In experiment 1 we showed the effects of proximity to the IceRods on temperature readings, which highlights the need for uniform probe placement. In experiment 2 we showed the effect of synergism and proximity to the cryoneedles. The probe 5 mm away from two cryoneedles achieved temperatures of $-75^\circ C$, whilst the probe 7 mm away from all four cryoneedles achieved a temperature of $-65^\circ C$. It is also evident from the graphs that not all points depict the same temperature. Some points are in the therapeutic range of $<-40^\circ C$ whilst others are not. This allows the possibility of inadequate treatment, with not all areas achieving a therapeutically low temperature. This also affects the assessment of the rectum with a single-sensor TMP. If the sensor is not placed at the point of lowest temperature, the risk of rectal injury will be higher. Single-sensor TMPs will not consistently detect this disparity, which might affect treatment outcomes. The multisensor TMPs allow a more thorough evaluation of the temperatures reached during treatment. Such accurate temperature monitoring will aid in the standardization of therapy, which would allow surgeons interested in this procedure to learn the technical aspects more quickly.

A comparison of experiments 1 and 2 highlights the synergistic effect of using several IceRods to achieve low temperatures. This is also true for the 17 G standard cryoneedle. The larger and longer ice-ball produced by the single IceRod needle will cover a larger area of the prostate, with lower temperatures reached with a higher freezing velocity.

We also showed that the length of the ice-ball achieved by eight IceRods is $\approx 6$ cm, greater than that achieved by SeedNet needles ($\approx 4$ cm) after 10 min of freezing (data not shown). This is useful in the treatment of prostates of $>3.5$ cm long a ‘pull-back’ technique, followed by a repeat of the freeze-thaw cycles, is needed, thus lengthening the procedure. It is well known that TRUS is not an accurate tool for measuring temperature during cryosurgery, and as 99% of the acoustic waves are reflected back by the ice-front, TRUS has limitations during the procedure [10]. The main use of TRUS is therefore two-fold; to guide the placement of the cryoneedles and TMPs, and to assess the ice-front in relation to the rectal wall. As a result, TMPs are crucial in cryotherapy, by constantly assessing the temperatures...
larger prostates, where the base to apex length is >3.5 cm, thus obviating the need for a ‘pull-back’ technique.

In the clinical setting the novel TMS multipoint TMPs were used in all 20 patients. The probes with four points of measurement were placed along the neurovascular bundles just outside the prostate, with another eight-point TMP placed in the recto-prostatic space. Single-point TMPs were placed within the prostate and another in the external urinary sphincter. The temperature within the prostate during the treatment was in the therapeutic range for all 20 patients (Fig. 5). The temperature in the external urinary sphincter did not fall below 0 °C at any point during treatment (data not shown). During the freezing cycles it was evident that the temperature recorded at each point on the three TMS probes differed (Fig. 6). This highlighted an important point, that when a single-point TMP is used, the accuracy and usefulness of the temperature reading depends on the position of the probe; there were marked variations in some points on the same probe just 1–2 cm apart. The changes in temperature in all eight points of the rectal probe were quite marked over the course of treatment (Fig. 7), which again highlights the disadvantage of a single-point TMP.

The present study clearly showed the variation in temperature in a longitudinal plane, highlighting a disadvantage of single-point TMPs. Correct placement is crucial to gain maximum information during the procedure. This clearly has implications for the effectiveness of cryotherapy. We have not used the multipoint TMPs within the prostate, but think that it would help with better monitoring during the procedure.

In conclusion, the IceRods and in particular the multisensor TMS probes are significant developments in prostate cryosurgery, with the potential to improve clinical outcomes with lower morbidity and better oncological results. The reliability and reproducibility of the temperatures reached during cryosurgery are crucial, and can be accurately monitored with using the TMS TMPs particularly in the recto-prostatic area. We think that this is an important development in the development of cryosurgery of the prostate, and will help to make it a safer and more reproducible procedure, and should also help clinicians to learn this technique more quickly.

CONFLICT OF INTEREST
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Abbreviations: TMP, temperature monitoring probe; TMS, temperature monitoring system.